Congestive Heart Failure Alters Receptor-Dependent cAMP-Mediated Relaxation of Canine Pulmonary Arteries

Rajamma Mathew, MD; Jie Wang, MD, PhD; Michael H. Gewitz, MD; Thomas H. Hintze, PhD; and Michael S. Wolin, PhD

Background. Alterations in myocardial function and systemic vascular tone are well documented in congestive heart failure (CHF), but little information is available on the effects of CHF on pulmonary vessels. We examined the mechanisms of tone regulation of canine pulmonary arteries during pacing-induced CHF.

Methods and Results. Rings 3–4 mm wide from lobar pulmonary arteries were prepared from normal dogs, dogs paced at 210 beats per minute for 3 weeks (paced group, nonfailure), and dogs also paced at 240 beats per minute during the fourth week to induce severe heart failure (CHF group). Contractile responses to 60 mmol/L KCl and phenylephrine and relaxation responses to acetylcholine, bradykinin (endothelium-dependent cyclic GMP [cGMP]-mediated), isoproterenol, arachidonic acid, prostacyclin (receptor-dependent cyclic AMP [cAMP]-mediated), forskolin (direct stimulator of adenylate cyclase), and forskolin analogue (devoid of adenylate cyclase-dependent activity), and RO 20-1724 (phosphodiesterase inhibitor) were characterized. The paced group did not show alterations in vascular reactivity. Contractile response to phenylephrine and cGMP-mediated relaxation responses were not altered in the CHF group; however, receptor-mediated cAMP-induced relaxation responses were significantly inhibited (p<0.05). Relaxation responses to isoproterenol (10^{-6} mol/L), arachidonic acid (10^{-5} mol/L), and prostacyclin (10^{-5} mol/L) were reduced by 56%, 72%, and 74%, respectively. The relaxation response to RO 20-1724 was not affected by CHF, and this probe did not enhance the impaired relaxation response to isoproterenol. Forskolin-induced relaxation was not altered, and the forskolin analogue produced minimal relaxation compared with forskolin.

Conclusions. These findings suggest that in pacing-induced CHF, canine pulmonary arteries show a selective defect in receptor coupling to cAMP-dependent relaxation mechanisms. There is no evidence of enhanced degradation of cAMP. (Circulation 1993;87:1722–1728)

KEY WORDS • isoproterenol • vascular reactivity, pulmonary • heart failure, congestive

Congestive heart failure (CHF) represents a clinical syndrome reflecting the inability of myocardium to meet the metabolic requirements of peripheral tissues. Alterations of vascular tone, low cardiac output, increased ventricular filling pressure, and pulmonary congestion are important components of CHF. In clinical and experimentally induced chronic heart failure, the myocardium has been found to be less sensitive to isoproterenol.1,2 In chronic CHF, vasomotor tone alterations have been noted in systemic vascular beds.3,4 However, scant information is available on the regulation of pulmonary vascular tone in CHF.

The aim of this investigation was to evaluate the effect of CHF on vascular tone and relaxation responses in isolated canine pulmonary arteries. We studied the contractile responses to KCl (60 mmol/L) and phenylephrine (PE). To evaluate receptor-mediated cyclic AMP (cAMP)-dependent responses, isoproterenol, arachidonic acid, and prostaglandin I2 (PGI2) were used. To assess adenylate cyclase activity, the effects of forskolin were examined. Forskolin, a diterpene compound, does not have an absolute requirement for a functional guanine nucleotide regulatory subunit to activate the catalytic unit of adenylate cyclase, although its ability to stimulate adenylate cyclase is enhanced in the presence of these proteins.5 Since forskolin is known to have adenylate cyclase-independent actions, the effects of a forskolin analogue (1',9'-dideoxyforskolin) that does not have adenylate cyclase–dependent activities6 was also examined. RO 20-1724, a specific cAMP phosphodiesterase inhibitor, was also used to assess whether there was an enhanced degradation of cAMP as a result of CHF. Finally, acetylcholine, bradykinin, and glyceryl trinitrate were used to evaluate cyclic GMP (cGMP)-mediated relaxation responses.

Methods

Mongrel dogs weighing 18–25 kg were instrumented with catheters, probes, and a corkscrew electrode in the left ventricle attached to a portable external pacemaker (Pace Medical EV3434, Waltham, Mass.) as described previously.2 Briefly, each dog was sedated with acepro-
mazine (1 mg/kg s.c.) and then anesthetized with sodium pentobarbital (25 mg/kg i.v.). A Tygon catheter (Cardiovascular Instruments, Wakefield, Mass.) was placed in the descending thoracic aorta, and a solid-state manometer (Konigsberg P6.5, Pasadena, Calif.) was placed in the left ventricle through the apex, using sterile surgical techniques. The dogs were allowed to recover from surgery for 7–10 days. Initial experiments were conducted when they were afebrile and had been trained to lie quietly without restraint on the laboratory table. The dogs were then paced at 210 beats per minute for 3 weeks (paced group). Some dogs were paced for an additional 1 week at 240 beats per minute to induce severe CHF (CHF group). The control group was similarly instrumented but not paced. A group of dogs without surgery was also studied. There were no differences in the pulmonary vascular reactivity in the two control groups; therefore, the data for these two groups were pooled. The protocols were approved by the Institutional Animal Care and Use Committee of New York Medical College and conform to the Guiding Principles for the Use and Care of Laboratory Animals of the American Physiological Society and the National Institutes of Health.

Cardiac Function Studies

Hemodynamic studies were performed with the dogs in a conscious state with the pacemaker turned off. Once the steady state was reached, the hemodynamic measurements were made. Systemic arterial pressure, left ventricular (LV) systolic pressure, LV end-diastolic pressure, LV dP/dt, and E\text{max}, were obtained. E\text{max}, the slope of the LV end-systolic pressure-volume relation, was determined from LV pressure-volume loop analysis. After hemodynamic data were obtained, the dogs were killed by an overdose of sodium pentobarbital. A thoracotomy was performed immediately, and the lungs were carefully removed and placed in cold Krebs bicarbonate buffer.

Isolated Pulmonary Artery Study

Second- and third-order branches of lobar pulmonary arteries were dissected and cleaned, taking care not to damage the endothelium, and 3–4-mm-wide rings were prepared. In some rings, the endothelium was deliberately removed by gentle rubbing of the luminal surface with a tapered wooden stick. Rings were mounted on steel wire hooks attached to a Grass (FT03) force displacement transducer at a basal tension of 6 g, and changes in isometric forces were recorded on Grass polygraph (model 7). Rings were allowed to equilibrate for 1 hour in Krebs bicarbonate buffer containing (in mmol/L) NaCl 118, KCl 4.7, CaCl\text{2} 1.5, NaHCO\text{3} 25, MgSO\text{4} 1.1, KH\text{2}PO\text{4} 1.2, and glucose 5.6 in individual 10-mL organ baths (Metro Scientific) maintained at 37°C and aerated with 95% \text{O}_2/5% \text{CO}_2 (pH 7.4). The rings were allowed to equilibrate in drug-free Krebs buffer for 30 minutes between the experimental cycles. The data were pooled for each type of vessel in each animal, and an average was calculated. Since acetylcholine, arachidonic acid, and bradykinin require intact endothelium, we analyzed endothelium-intact arteries for all the groups.

Evaluation of Contractile Responses

Arterial rings from all groups were depolarized with 60 mmol/L KCl for 5 minutes, and the steady-state tone was recorded. After a 30-minute equilibration in Krebs buffer, the dose response to PE (10\text{-8} to 10\text{-6} mol/L) was obtained, and in four additional animals from each of the control and CHF groups, dose response to PE (10\text{-8} to 10\text{-4} mol/L) was obtained. For subsequent experiments, a submaximal dose of PE (10\text{-7} to 10\text{-5} mol/L) that produced about 40–50% of maximal contraction was used.

Evaluation of cGMP-Mediated Responses and the Integrity of the Endothelium

Dose response to acetylcholine (10\text{-8} to 10\text{-5} mol/L) was obtained to assess the functional integrity of the endothelium after dose response to PE. After 30 minutes of equilibration in drug-free Krebs buffer, the arterial rings were precontracted with PE, and once the steady-state tone was reached, a dose response to bradykinin (10\text{-8} to 10\text{-6} mol/L) was obtained. Two rings from each animal were incubated in indomethacin (10\text{-5} mol/L) for 10 minutes, and relaxation response to bradykinin was reassessed. In precontracted, endothelium-denuded arterial rings, the relaxation response to cumulative doses of glyceryl trinitrate (10\text{-9} to 10\text{-6} mol/L) was recorded.

Evaluation of Receptor-Mediated cAMP-Dependent Relaxation Responses

The arterial rings were precontracted as described earlier with PE, and relaxation responses to isoprotenerol (10\text{-8} to 10\text{-6} mol/L) or arachidonic acid (10\text{-8} to 10\text{-5} mol/L) were obtained. Two rings from each animal were incubated in 10\text{-5} mol/L indomethacin for 15 minutes, and the relaxation response to arachidonic acid was repeated. To determine whether the defect in arachidonic acid-induced relaxation observed in CHF was receptor-mediated or secondary to endothelial cell dysfunction, the relaxation response to PGI\text{2} (10\text{-8} to 10\text{-5} mol/L) was also examined in control and failure groups.

Evaluation of Direct Stimulation of Adenylate Cyclase

To evaluate whether the level of defect seen in CHF was at the receptor G protein level or at the level of the catalytic unit of adenylate cyclase, the relaxation response to forskolin (10\text{-8} to 10\text{-5} mol/L) was examined in control and failure groups. A protocol similar to that for isoprotenerol was used. Similarly, response to 1',9'-dideoxyforskolin (a forskolin analogue) (10\text{-8} to 10\text{-5} mol/L) was recorded on precontracted pulmonary arterial rings in control and heart failure groups (n=4, each group), and simultaneously, the response to forskolin was also obtained on rings from each animal for comparison within the group.

Evaluation of cAMP-Dependent Phosphodiesterase Activity

To assess whether enhanced degradation of cAMP was responsible for the observed alterations in cAMP-dependent relaxation responses, we examined the effects of RO 20-1724, a cAMP-specific phosphodiesterase inhibitor. Rings were initially precontracted, and response to isoproterenol (10\text{-7} mol/L) was recorded. Rings were then...
Materials

PE HCl, isoproterenol HCl, acetylcholine chloride, and bradykinin acetate were obtained from Sigma Chemical Co. (St. Louis, Mo.) and dissolved in deionized water to obtain 10^-2 mol/L stock solutions, except bradykinin (10^-3 mol/L). Arachidonic acid (Sigma) was dissolved in 100 mmol/L Na_2CO_3, and deionized water was added to obtain a final solution of 10^-2 mol/L in 10 mmol/L Na_2CO_3; this was collected in small aliquots under nitrogen and stored at -80°C. Further dilutions were made in deionized water just before use. Prostacyclin (Upjohn Co., Kalamazoo, Mich.) was dissolved in Tris buffer (pH 8), and it was used within half an hour. Forskolin, 1',9'-dideoxyforskolin (Calbiochem Co., La Jolla, Calif.), RO 20-1724 ( Biomol Research Laboratories, Inc., Plymouth Meeting, Pa.), and indomethacin (Sigma) were dissolved in absolute ethyl alcohol to obtain 10^-2 mol/L stock solutions. Further dilutions were made in ethyl alcohol. Glycerol trinitrate was dissolved in deionized water on the day of use. During the experiments, the drug solutions were kept on ice.

Statistical Analysis

The results are expressed as mean ± SEM. The groups were assessed by ANOVA, Scheffe’s multiple comparison test, and two-tailed Student’s t test, as appropriate. A value of p < 0.05 was considered statistically significant. The resting tension was defined as 0, and measurements are presented as active force generated above the baseline. The relaxation response is expressed as percent decrease in tone in relation to the initial tone induced by PE.

Cardiac Function

Animals in the failure group gained weight, and all of them displayed clinical symptoms and signs of CHF, including tachycardia (pacemaker off), tachypnea, ascites, pulmonary congestion, and pleural effusion. The control and the paced (without failure) groups were free of these symptoms. As shown in Table 1, myocardial function was significantly affected. Tachycardia, low systemic arterial pressure, elevated LV end-diastolic pressure, and decreased LV dP/dt were present in paced dogs without overt failure, and further deterioration in myocardial function was observed in the failure group. E_max, however, was within normal limits in the paced group, but it was depressed in the failure group, as has been shown earlier. Prior studies from our laboratory have shown the myocardial response to isoproterenol infusion to be significantly inhibited during CHF.

Results

Table 1. Hemodynamic Parameters in Heart Failure Dogs

<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th>Paced group</th>
<th>CHF group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td>73±2</td>
<td>95±2*</td>
<td>125±3*†</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>99±1</td>
<td>94±1*</td>
<td>85±2*†</td>
</tr>
<tr>
<td>LV systolic pressure (mm Hg)</td>
<td>137±3</td>
<td>114±2*</td>
<td>104±4*†</td>
</tr>
<tr>
<td>LV end-diastolic pressure (mm Hg)</td>
<td>7.5±0.7</td>
<td>11.5±0.6*</td>
<td>24±2*†</td>
</tr>
<tr>
<td>LV dP/dt (mm Hg/sec)</td>
<td>3,112±122</td>
<td>1,889±54*</td>
<td>1,432±71*†</td>
</tr>
<tr>
<td>E_max (mm Hg/mm)</td>
<td>44±3.6</td>
<td>40±4.5</td>
<td>19±1.7*†</td>
</tr>
</tbody>
</table>

Table 1: Hemodynamic Parameters in Heart Failure Dogs

CHF, congestive heart failure; bpm, beats per minute; LV, left ventricular.

*p<0.05 vs. control; †p<0.05 vs. paced.

Contractile Responses

As shown in Figure 1, the contractile response to PE was not altered in any of the groups (paced group not shown). The maximum tone developed with 60 mmol/L KCl was not significantly different in any of the groups. They were 3.2±0.4, 3.2±0.3, and 3.0±0.4 g for control (n=6), paced (n=5), and heart failure (n=7) groups, respectively.

cGMP-Mediated Relaxation Responses

As shown in Figures 2 and 3, the endothelium-dependent relaxation responses to acetylcholine and bradykinin were not affected in any of the groups. The response to bradykinin was confirmed to be endothelium dependent, and indomethacin had no effect on this response (data not shown). The relaxation to glyceryl trinitrate was not altered in any of the groups (data not shown).

Receptor-Mediated cAMP-Dependent Relaxation Responses

In a dose range of 10^-8 to 10^-6 mol/L isoproterenol, there were no significant differences in relaxation responses between the control and the paced groups. In
the heart failure group, however, isoproterenol-induced relaxation was significantly \((p<0.05)\) inhibited, as shown in Figure 4. For instance, a concentration of 10^{-8} mol/L caused 48±5% and 44±7% relaxation in control and paced (without failure) groups, respectively, but only 21±5% relaxation in pulmonary arteries from dogs with CHF. Similarly, the relaxation response to arachidonic acid was not statistically different between control and paced without failure groups. As depicted in Figure 5, this response was markedly inhibited in the CHF group. The relaxation response to arachidonic acid was endothelium-dependent and was abolished by indomethacin (data not shown). Significant \((p<0.05)\) inhibition of the relaxation response to PGI\(_2\) during CHF was noted, as shown in Figure 6.

**Relaxation Response to Forskolin**

As seen in Figure 7, the relaxation response to forskolin was significantly increased at a low dose of 10^{-8} mol/L in pulmonary arteries from dogs with CHF; with subsequent higher doses, however, there were no differences between the control and failure groups. The forskolin analogue did not produce any relaxation at low doses \((10^{-8} \text{ to } 10^{-7} \text{ mol/L})\). At 10^{-8} mol/L concentration, it produced 12±7% and 10±3% relaxation in control \((n=4)\) and failure \((n=4)\) groups, respectively \((p=NS)\), and at 10^{-5} mol/L concentration it produced 25±18% and 38±9% relaxation in control and CHF groups, respectively \((p=NS)\). Relaxation responses to forskolin and forskolin analogue were significantly different at each concentration level in each group \((p<0.05)\).

**Actions of cAMP-Selective Phosphodiesterase Inhibitor**

The addition of 10^{-7} mol/L isoproterenol to precontracted rings from the control group \((n=4)\) produced 36±7% relaxation, whereas in the CHF group \((n=4)\), the response was only 11±6% \((p<0.05)\). The addition
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![Graph showing relaxation response to prostaglandin I2 (PGI2) in isolated pulmonary arteries from control and congestive heart failure (CHF) dogs.](image1)

**Figure 6.** Graph showing relaxation response to prostaglandin I2 (PGI2) in isolated pulmonary arteries from control and congestive heart failure (CHF) dogs. Relaxation responses are expressed as percent decrease in tone from the phenylephrine-induced tone. Note that there is significant inhibition of relaxation response to PGI2 in the CHF group. *p<0.05 vs. control.

of RO 20-1724 (10^-5 mol/L) to precontracted rings produced 23±5% relaxation in the control group (n=4) and 19±5% in the CHF group (n=8). The addition of 10^-7 mol/L isoproterenol produced a further relaxation of 44±10% in the control group and only 14±7% in the CHF group (p<0.05). Tachyphylaxis to isoproterenol was not observed in these experiments.

**Discussion**

This study demonstrates the effects of pacing-induced CHF on the reactivity of isolated canine pulmonary arteries. Hemodynamic responses and the clinical and pathological features in pacing-induced CHF are similar to those present in naturally occurring CHF in humans. Altered vascular responses to physiological stimuli during CHF are thought to be secondary to neural, humoral, and local factors. In the paced group without clinical signs and symptoms of failure, despite poor myocardial function, pulmonary vascular reactivity remained normal, as shown in Table 1 and Figures 2-5. With further deterioration of myocardial function and the development of clinical syndrome of CHF, concomitant alterations in pulmonary vascular reactivity occurred. Thus, the vascular reactivity in isolated pulmonary arteries appears to be affected when clinically apparent heart failure is present with deteriorating myocardial function and pulmonary congestion. This observation would suggest that these pulmonary vascular changes occur when pulmonary congestion appears.

Peripheral vasoconstriction is an important feature of CHF. Although impaired peripheral sympathetic vasoconstriction has been demonstrated, contractile responses to norepinephrine in the systemic arteries are not altered. This observation is consistent with our present studies of pulmonary arteries, in which the contractile response to PE remained unaltered.

In response to acetylcholine and bradykinin, endothelial cells release an endothelium-derived relaxing factor (EDRF), considered to be nitric oxide, that activates intracellular guanylate cyclase, resulting in increased cGMP and smooth muscle relaxation. In this study, relaxation responses to acetylcholine and bradykinin were not significantly different in the CHF group compared with the control group. Thus, EDRF-mediated relaxation responses do not appear to be altered in pulmonary arteries in pacing-induced CHF. Our findings, however, are different from those observed by Ontkeane et al. in rat pulmonary arteries. These authors have shown that after CHF induced by myocardial infarction, the EDRF-mediated relaxation response to acetylcholine is diminished. Diminished EDRF-mediated relaxation response to acetylcholine in canine femoral arteries in CHF has also been reported, and its response is enhanced by indomethacin, suggesting that prostaglandins may be involved. In another study, we found enhanced endothelium-dependent relaxation in coronary arteries from the paced group without heart failure, as did O'Murchu et al. The differences in these observations could be dependent either on species or on the arterial segments examined.

The most important finding of our study is the inhibition of receptor-mediated stimulation of adenylate cyclase. The relaxation response to isoproterenol was significantly depressed in pulmonary arteries, which is similar to observations in the myocardium in CHF by others. Isoproterenol, via β-adrenergic receptors, mediates vascular smooth muscle relaxation and vasodilation in pulmonary and systemic vascular beds. This process is considered to be coupled to the activation of adenylate cyclase via stimulatory guanine nucleotide binding proteins (G_s), leading to increased intracellular cAMP. In the failing human ventricular myocardium, downregulation of β-adrenergic receptors and a decrease of myocardial β-adrenergic receptors in the high-affinity state have been demonstrated, suggesting that catecholamines have a reduced ability to trigger an appropriate increase in cAMP and subsequent inotropic response. Our data show that the relaxation responses to arachidonic acid and PGI2 are also significantly reduced in CHF. Arachidonic acid is primarily converted to PGI2 by the vascular endothelium. The initial step in biological responses to PGI2 is binding to

![Graph showing relaxation response to forskolin.](image2)

**Figure 7.** Graph showing relaxation response to forskolin, expressed as percent decrease in tone from phenylephrine-induced tone in isolated pulmonary arteries from control and congestive heart failure (CHF) dogs. Note that there is significant increase in relaxation response in the CHF group to a small dose (10^-9 mol/L); however, there are no significant differences at higher doses. *p<0.05 vs. control.
a specific PG12 receptor, which is coupled to the adenylyl cyclase system via a G protein.19 In this context, it is worth noting that catecholamine as well as prostaglandin levels are increased in CHF.20,21,22 Thus, diminished β-receptor− and PG12-mediated responses may originate from the desensitization of each of these receptors by elevated levels of catecholamines and prostaglandins. Alternatively, these defects could be secondary to alterations in guanine nucleotide binding proteins. Reithmann et al23 have reported that prolonged treatment of cultured rat heart muscle cells with norepinephrine leads to heterologous desensitization secondary to an increase in level and activity of the adenylyl cyclase G inhibitory (G) protein. In dogs during heart failure induced by pressure overload of the left ventricle, there is evidence that G, in the myocardium is decreased, and in the failing human heart, there is enhanced activity of G.24,25 Thus, the mechanism underlying inhibition of multiple receptor-mediated stimulation of adenylyl cyclase could be an abnormality of guanine binding proteins. However, no information is currently available on the status of G proteins in pulmonary arteries during CHF.

Forskolin-induced relaxation, interestingly, is not affected by CHF, as shown in Figure 7. At a low dose of 10 nmol/L forskolin, there is significantly increased relaxation in the CHF group compared with the control group. The reason for this enhanced relaxation is not clear, but it could be related to alterations in the activity of G proteins during CHF, since it is well established that G proteins can influence the effects of forskolin.5 The forskolin analogue retains much of the activity of forskolin (such as regulation of ion channels and phosphodiesterase inhibition), but it does not stimulate adenylyl cyclase.5 Our data show that the forskolin analogue can cause modest relaxation at high concentrations, but its actions are markedly less than that of forskolin itself. In addition, the modest relaxation response to this analogue was not significantly different between the control and CHF groups. These observations are consistent with forskolin producing relaxation of canine pulmonary arteries primarily via an adenylyl cyclase−dependent mechanism and indicate that this mechanism does not appear to be affected during pacing-induced CHF. Recently it has been shown that there is a defect in the catalytic unit of adenylyl cyclase in myocardial membranes obtained from dogs with pacing-induced CHF as well as from humans with clinical CHF. The basal and stimulated adenylyl cyclase activities have been found to be low, and these changes are chamber-specific and considered to be dependent on local effects. It has been proposed that these decreases in adenylyl cyclase activity could partially be caused by a generalized membrane dysfunction, independent of G proteins.26−28 Differences between the previous studies and ours might be dependent on a time factor. If the pulmonary arteries had been studied after a longer duration of CHF, we might also have observed generalized membrane dysfunction. In this context, it is interesting to note that in the paced group, despite significant myocardial dysfunction, the vascular reactivity in pulmonary arteries was not affected.

Relaxation to the cAMP-selective phosphodiesterase inhibitor RO 20-1724 was not significantly different in the CHF group compared with controls, suggesting that basal cAMP levels are not affected in CHF. In addition, the presence of this cAMP-selective phosphodiesterase inhibitor did not enhance response to isoproterenol in the CHF group, in line with depressed synthesis and not because of increased degradation of cAMP. Our studies with forskolin and RO 20-1724 are consistent with normal catalytic function of adenylyl cyclase and basal cAMP levels in canine pulmonary arteries during pacing-induced CHF. Further biochemical assays of adenylyl cyclase activity are necessary to substantiate this hypothesis. There appears to be a decrease in the ability of canine pulmonary arteries during pacing-induced CHF to relax in response to adrenergic and prostaglandin stimulation. These observations indicate that there is heterologous desensitization of receptors linked to the stimulation of adenylyl cyclase, which is likely to originate from a defect in receptor-mediated G protein−linked signal transduction.

In summary, we have demonstrated that β-adrenergic receptor− and PG12 receptor−mediated relaxation responses are inhibited in canine pulmonary arteries during CHF and that this effect is not caused by a generalized depression of pulmonary artery relaxation responses, since cGMP-mediated relaxation responses remained normal. This relaxation defect appears to be specific for receptor-mediated cAMP-induced relaxation mechanisms. In addition, the origin of the defect in CHF does not appear to involve cAMP-selective phosphodiesterase activity.

References

Congestive heart failure alters receptor-dependent cAMP-mediated relaxation of canine pulmonary arteries.

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