Voltage-Dependent Calcium Channel Promoter Restores Baroreflex Sensitivity in Conscious Dogs With Heart Failure

Masami Uechi,* DVM, PhD; Kuniya Asai,* MD; Naoki Sato, MD; Stephen F. Vatner, MD

Background—The aim of this study was to determine the mechanism by which the calcium channel promoter BAY y 5959 affects the control of heart rate and baroreflex sensitivity in conscious dogs with pacing-induced heart failure (HF).

Methods and Results—We compared responses to BAY y 5959, which increases inotropy and decreases chronotropy, with those to norepinephrine (NE), which coincidentally exerts the same directional effects on inotropy and chronotropy, albeit through different mechanisms, in the presence and absence of ganglionic blockade both in control and in HF. Both BAY y 5959 and NE elicit direct effects on the heart and indirect effects through activation of reflexes, primarily the sinoaortic baroreceptor reflex. BAY y 5959 still reduced heart rate in dogs with arterial baroreceptor denervation, but not after ganglionic blockade. HF induced classic catecholamine desensitization to the inotropic effects of NE and blunted reflex bradycardia. In contrast, inotropic responses to BAY y 5959 were preserved in HF. Surprisingly, the autonomically mediated bradycardia induced by BAY y 5959 was also preserved in HF. Baroreflex sensitivity was assessed in control and in HF by pulse interval–systolic arterial blood pressure (PI/SAP) slopes constructed in response to pharmacological alterations in arterial pressure. HF depressed the PI/SAP slope from 11.5±1.3 to 4.8±0.9 ms/mm Hg, but during BAY y 5959 infusion in HF, the PI/SAP slope was restored to 24.1±5.2 ms/mm Hg. To assess central versus peripheral actions of BAY y 5959, the agent was infused with intra–carotid artery perfusion at a low dose, which acted centrally but did not have an effect peripherally. Under these conditions, it still decreased heart rate and restored baroreflex sensitivity (PI/SAP slope, 12.7±2.8 ms/mm Hg).

Conclusions—Thus, the calcium promoter restores arterial baroreflex sensitivity in HF. Based on intra–carotid artery experiments, this occurs through a central nervous system and vagal mechanism. (Circulation. 1998;98:1342-1347.)

Key Words: dihydropyridine • nervous system • bradycardia

Blunted baroreflex sensitivity is characteristic of experimental1 and clinical2 heart failure. Because the blunted baroreflex sensitivity and reduced heart rate variability in heart failure correlate with mortality,3-4 preservation of baroreflex sensitivity may be clinically important. The extent to which blunted arterial baroreflex sensitivity is reversible in heart failure remains controversial. Several studies have shown partial recovery of arterial baroreflex function with improved hemodynamics induced acutely by reduction in preload and afterload5 or more chronically by removal of the stimulus to heart failure.6 Other studies have implicated alterations in ionic control of baroreceptors as the mechanism for dysfunction in heart failure.7 8 Although it is clear that calcium can regulate baroreflex function, the extent to which calcium activation9 or administration of calcium antagonists affects baroreflex control in heart failure also remains controversial.10-13

One goal of the present investigation was to determine the regulation of heart rate by augmenting calcium levels either systemically with intravenous (IV) infusion or selectively in the brain with intra–carotid artery infusion of a calcium promoter to conscious dogs before and after induction of pacing-induced heart failure. The calcium promoter BAY y 5959 was selected for study because it is well tolerated by conscious animals and is relatively devoid of vascular effects.14 The drug increases both the mean open time and mean closed time of the Ca$^{2+}$ channel by binding dihydropyridine receptors in a voltage-dependent manner, resulting in a reduced rate of Ca$^{2+}$ current activation, increased peak current, and a prolonged tail-current decay.15 The calcium promoter, while increasing myocardial contractility by a direct mechanism, reduces heart rate by an indirect, autonomic mechanism, ie, after either ganglionic blockade or atropine the bradycardia is abolished in normal, conscious dogs without heart failure. Interestingly, BAY y 5959 was found to elicit the same bradycardia in heart failure as observed in normal conscious dogs without heart failure (unpublished observations). This would imply that the blunted arterial baroreflex sensitivity characteristic of heart failure was not observed during the infusion of the calcium promoter. Accordingly, the second goal of the present investigation was to determine the effects of the calcium promoter...
on baroreflex sensitivity in heart failure. To achieve this goal, baroreflex sensitivity was assessed by pulse interval–systolic arterial pressure (PI/SAP) slopes in conscious dogs in control and in heart failure.

In addition, the inotropic and chronotropic effects of BAY y 5959 were compared with those of norepinephrine, a catecholamine that, like the calcium channel promoter, decreases heart rate while increasing myocardial contractility. However, norepinephrine reduces heart rate almost entirely through the arterial baroreflex. To evaluate the reflex components of their action, experiments were repeated in the presence and absence of chronic sinoaortic arterial baroreceptor denervation (SAD) and in the presence and absence of ganglionic blockade. Ganglionic blockade was used to verify that the mechanism was neurally mediated. Experiments after SAD were used to pinpoint the role of the arterial baroreflex in mediating the response to BAY y 5959. In addition, to assess the potential central neural regulation of baroreflex sensitivity by the calcium promoter, additional experiments were conducted in conscious dogs with heart failure, in which small quantities of BAY y 5959 were infused to the brain through chronically implanted carotid arterial catheters. These latter experiments were particularly important because alterations in systemic hemodynamics, which could affect arterial baroreflex function per se, were avoided by the trivial levels of drug used, which were well below the threshold for systemic hemodynamic effects. Finally, the effenter mechanism of the bradycardia induced by BAY y 5959 was determined by examining the effects of the calcium promoter in the presence and absence of β-adrenergic receptor blockade with propranolol and muscarinic receptor blockade with atropine before and after development of heart failure.

Methods

Surgical Preparations

Eight adult mongrel dogs of either sex were anesthetized with halothane (1.0 to 1.5 vol%) and ventilated with a Harvard respirator after induction with thiopental (10 to 20 mg/kg IV). A left thoracotomy was performed through the fifth intercostal space with a sterile technique. Tygon catheters (Norton Elastic and Synthetic Division) were placed into the descending thoracic aorta and left atrial appendage. A solid-state miniature pressure transducer (P6, Konigsberg Instruments) was implanted through the left ventricular (LV) apex to measure LV pressure. A screw-in–type pacing lead was attached to the right ventricular free wall, and stainless steel pacing wires were placed on the left atrium. The catheters and lead wires were tunneled subcutaneously to the back of the neck, and the thoracotomy was closed.

In 6 dogs, SAD was performed at the time of instrumentation. Briefly, the aorta was stripped of all nerve fibers and connective tissue from the aortic root to the second intercostal artery. The brachiocephalic and the subclavian arteries were also stripped from the aorta cranially to the second set of branches. Carotid sinus denervation was performed after aortic baroreceptor denervation. Through a midline incision in the ventral cervical region, the right and left common carotid arteries were isolated and stripped of nerve fibers and connective tissue 2 to 3 cm distal to the bifurcation of the internal and external carotid arteries. The denervation was confirmed by absence of reflex heart rate in response to phenylephrine (5 to 10 μg/kg IV) and nitroglycerin (5 to 10 μg/kg IV). In 4 SAD dogs, a 6F micromanometer catheter (Millar Instruments) was introduced via the femoral artery to measure LV pressure and LV dP/dt.

In 5 dogs, internal carotid artery catheters were implanted after the induction of heart failure. Through a midline incision in the ventral cervical region, the right and left common carotid arteries were isolated, and Silastic catheters (0.625-mm external diameter) were advanced to the internal carotid artery. All dogs were allowed to recover for at least 2 weeks before experimentation and were treated with 1.0 g cephalothin for 10 days after surgery. All animals used in these studies were maintained according to the Guide for the Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (NIH publication 93-23, revised 1985) and the Standing Committee on Animal Care of Harvard Medical School.

Experimental Protocols

Experiments were conducted in the control state, before pacing, and after heart failure had developed. Dogs were studied in the conscious state while lying quietly on their right side. All hemodynamic measurements were recorded in sinus rhythm, after a 20- to 30-minute stabilization period after the pacemaker was turned off. The aortic and left atrial catheters were connected to strain-gauge manometers (Statham Instruments) for measurements of arterial and left atrial pressures. LV pressure and its first derivative (dP/dt) were measured with the miniaturized pressure gauge, and the ECG was recorded. All hemodynamic measurement data were recorded on a multichannel tape recorder (Honeywell) and played back on a direct-writing oscillograph (Gould-Brush). Heart failure, characterized by ascites and exercise intolerance, was induced by right ventricular pacing at 240 bpm for 3 to 5 weeks with a programmable pacemaker (model EV4543, Pace Medical) that was worn externally in a vest.

BAY y 5959 ([α]-isopropyl-2-amino-5-cyano-1,4-dihydro-6-methyl-4-(3-phenylquinoline-5-yl)-pyridine-3-carboxylate) was administered as 10-minute graded IV infusions of 5, 10, and 20 μg · kg⁻¹ · min⁻¹ via a peripheral vein while measurements of LV pressure, LV dP/dt, mean arterial pressure, left atrial pressure, and heart rate were recorded. Norepinephrine was administered as 5-minute graded IV infusions of 0.05, 0.1, and 0.2 μg · kg⁻¹ · min⁻¹. The infusion regimen for each drug was determined by preliminary studies. Because hemodynamic responses were in the steady state 10 minutes after infusion of BAY y 5959 and 5 minutes after infusion of norepinephrine, these times were selected for data analysis, whereas the concentrations were selected to achieve roughly equi-inotropic effects of the 2 agents after ganglionic blockade. On a separate day, the same doses of BAY y 5959 and norepinephrine were repeated in the presence of ganglionic blockade with hexamethonium bromide (30 mg/kg IV) and atropine (0.1 mg/kg IV). The efficacy of blockade was confirmed by the absence of reflex heart rate responses to arterial pressure changes induced by administration of nitroglycerin (5 μg/kg IV). In 6 dogs before heart failure and in 3 dogs with heart failure, the efferent mechanism of the bradycardia induced by BAY y 5959 was examined on separate days after β-adrenergic receptor blockade with propranolol (1 mg/kg IV) or atropine (0.1 mg/kg IV). Baroreflex sensitivity was assessed in 7 dogs before and after pacing-induced heart failure by plotting PI/SAP slopes. The PI/SAP slopes were analyzed by relating the change in systolic pressure induced by phenylephrine (5 to 20 μg/kg IV) and nitroglycerin (5 to 20 μg/kg IV) to the reflex change in R-R interval. These slopes were calculated in control and in heart failure were also examined during infusion of BAY y 5959 (20 μg · kg⁻¹ · min⁻¹ IV). These protocols were repeated in the same dogs with heart failure. In 5 dogs with heart failure, BAY y 5959 (0.0025 to 0.005 μg · kg⁻¹ · min⁻¹ over 10 minutes) was also administered through intra–internal carotid artery catheters while measurements of heart rate, LV pressure, LV dP/dt, and mean arterial pressure were recorded.

Data Analysis

All data are expressed as mean±SEM. Because the same animals were used to compare the effects of the 2 agents in the absence and presence of ganglionic blockade, a repeated-measures ANOVA procedure of Super ANOVA (Abacus Concepts) was used to
TABLE 1. Baseline Hemodynamics in Control State and With Heart Failure

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Control</th>
<th>Heart Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, bpm</td>
<td>8</td>
<td>97±3</td>
<td>121±7*</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>8</td>
<td>89±4</td>
<td>77±3*</td>
</tr>
<tr>
<td>LVSP, mm Hg</td>
<td>8</td>
<td>111±6</td>
<td>104±7</td>
</tr>
<tr>
<td>LV EDP, mm Hg</td>
<td>8</td>
<td>5±1</td>
<td>22±2*</td>
</tr>
<tr>
<td>LV dP/dt, mm Hg/s</td>
<td>8</td>
<td>2948±128</td>
<td>1517±112*</td>
</tr>
</tbody>
</table>

*MAP indicates mean arterial pressure; LVSP, LV systolic pressure; and EDP, end-diastolic pressure.

‡Change from baseline with heart failure different from control, P<0.05 vs control.

Effects of BAY y 5959 on Heart Rate in the Presence of Either β-Adrenergic Receptor or Muscarinic Blockade

Atropine blocked the decreases in heart rate entirely with BAY y 5959 in the control state, but with heart failure, BAY y 5959 still reduced heart rate by 11±4 bpm after atropine (P<0.05 versus before heart failure). In the presence of propranolol, BAY y 5959 reduced heart rate by 27±4 bpm in control and tended to reduce heart rate less, by 18±3 bpm, with heart failure.

Effects of BAY y 5959 in SAD Dogs

In conscious SAD dogs, nitroglycerin decreased mean arterial pressure by 40±3 mm Hg but did not change heart rate.

TABLE 2. LV Effects of NE (0.2 μg·kg⁻¹·min⁻¹) in Control State and With Heart Failure With and Without Ganglionic Blockade (n=7)

<table>
<thead>
<tr>
<th></th>
<th>Control Intact</th>
<th>Baseline</th>
<th>∆ NE</th>
<th>Heart Failure</th>
<th>Baseline</th>
<th>∆ NE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, bpm</td>
<td>103±4</td>
<td>121±4</td>
<td>+18±5*†</td>
<td>123±4</td>
<td>124±5</td>
<td>+6±1*‡</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>96±3</td>
<td>78±3</td>
<td>+73±13 †</td>
<td>84±4</td>
<td>70±2</td>
<td>+37±10 †‡</td>
</tr>
<tr>
<td>LV peak systolic pressure, mm Hg</td>
<td>119±5</td>
<td>96±3</td>
<td>+85±14 †</td>
<td>103±5</td>
<td>87±3</td>
<td>+35±10†‡</td>
</tr>
<tr>
<td>LV end-diastolic pressure, mm Hg</td>
<td>10±1</td>
<td>6±1</td>
<td>+5±2</td>
<td>21±2</td>
<td>19±1</td>
<td>+6±2*</td>
</tr>
<tr>
<td>LV dP/dt, mm Hg/s</td>
<td>294±132</td>
<td>2516±105</td>
<td>+3920±690*†</td>
<td>1713±135</td>
<td>1484±107</td>
<td>+869±237†‡</td>
</tr>
</tbody>
</table>

*Values are mean±SEM.

Change from baseline, P<0.05.

†Change from baseline after ganglionic blockade different from intact, P<0.05.

‡Change from baseline with heart failure different from control, P<0.05.
TABLE 3. LV Effects of BAY y 5959 (20 μg · kg⁻¹ · min⁻¹) in Control State and Heart Failure With and Without Ganglionic Blockade (n=8)

<table>
<thead>
<tr>
<th></th>
<th>Control Heart Failure</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline Δ BAY</td>
<td>Baseline Δ BAY</td>
<td>Baseline Δ BAY</td>
</tr>
<tr>
<td>---------------------</td>
<td>-----------------------</td>
<td>---------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>122±6</td>
<td>122±6</td>
<td>122±6</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>4.0±1†</td>
<td>25±4*†</td>
<td>4.8±1</td>
</tr>
<tr>
<td>LV peak systolic pressure, mm Hg</td>
<td>23±4*†</td>
<td>34±3*‡</td>
<td>24.1±3*</td>
</tr>
<tr>
<td>LV end-diastolic pressure, mm Hg</td>
<td>7±3</td>
<td>11±2</td>
<td>19±2</td>
</tr>
<tr>
<td>LV dP/dt, mm Hg/s</td>
<td>2387±358‡</td>
<td>1428±144*</td>
<td>2015±238*‡</td>
</tr>
</tbody>
</table>

BAY indicates BAY y 5959. Values are mean±SEM.
*Change from baseline, P<.05.
†Change from baseline after ganglionic blockade different from intact, P<.05.
‡Change from baseline with heart failure different from control, P<.05.

Phenylephrine increased mean arterial pressure by 47±5 mm Hg but did not change heart rate. These experiments confirmed the adequacy of SAD dogs. However, BAY y 5959 at a dose of 20 μg · kg⁻¹ · min⁻¹ decreased heart rate (–23±4 bpm) in SAD dogs, whereas mean arterial pressure increased by 23±8 mm Hg (Figure 1).

Alteration of Baroreflex Sensitivity With BAY y 5959

The PI/SAP slope constructed in response to blood pressure changes induced by phenylephrine and nitroglycerin was decreased with heart failure (4.8±0.9 ms/mm Hg, n=5) compared with control (11.5±1.3 ms/mm Hg, n=5) (Figure 2). In the presence of BAY y 5959, the PI/SAP slope was significantly increased in control (33.6±9.9 ms/mm Hg, P<.05) and with heart failure (24.1±5.2 ms/mm Hg, P<.05).

Effects of Intra–Carotid Arterial BAY y 5959 Infusion

Heart rate fell by 15±6 bpm in response to intra–carotid artery BAY y 5959 infusion. However, heart rate was not changed while the same dose of BAY y 5959 was infused systemically. Mean arterial pressure and LV dP/dt were not affected by either intra-carotid artery or IV BAY y 5959 infusion at this low dose. The PI/SAP slope was similar during IV BAY y 5959 infusion at this low dose (5.0±0.4 ms/mm Hg) and in heart failure in the absence of drug infusion (4.8±0.5 ms/mm Hg) (Figure 3). However, intra-carotid artery low-dose BAY y 5959 infusion increased the
By guest on April 18, 2017 http://circ.ahajournals.org/ Downloaded from

The bradycardia in response to norepinephrine is mediated by the arterial baroreceptor reflex. The first goal of the present investigation was to determine the mechanism of the bradycardia in response to the calcium promoter. Because the bradycardia was completely abolished by ganglionic blockade, we concluded that the bradycardia was neurally mediated and not due to a direct effect of the drug. However, because the bradycardia was not abolished in the dogs with SAD, a baroreflex mechanism was not entirely responsible for the autonomously mediated bradycardia. These data, taken in combination, suggest that the bradycardia in response to the calcium promoter was mediated to a major extent by a central neural mechanism. Potentially, the drug could act to increase vagal nerve activity, a mechanism consistent with the findings that the bradycardia was abolished by ganglionic blockade but not by SAD. In further support of this concept, intra–carotid artery infusions of small quantities of BAY y 5959 elicited bradycardia without increasing arterial pressure. However, when the same dose of the drug was administered systemically, no effects on hemodynamics or heart rate were observed. Furthermore, in control dogs, the bradycardia was abolished with atropine, whereas in the presence of heart failure, a component of the bradycardia, presumably due to sympathetic withdrawal, persisted after muscarinic blockade. This suggests that a component of the efferent bradycardia in heart failure with the afferent loop in the central nervous system is mediated by sympathetic withdrawal. A parallel situation occurs with the arterial baroreflex control of heart rate, which is almost entirely vagal in the control state but includes a component of sympathetic withdrawal in heart failure.10

The fact that the calcium promoter elicited the same bradycardia in the presence and absence of heart failure implied that the well-known blunted arterial baroreflex sensitivity characteristic of heart failure was actually preserved during BAY y 5959 infusion. To confirm that depressed baroreflex sensitivity occurred in the model of pacing-induced heart failure,7 we examined PI/SAP slopes in response to pharmacologically induced hypotension and hypertension. As expected, the PI/SAP slopes were depressed in heart failure. Surprisingly, the PI/SAP slope, ie, baroreflex sensitivity, was not only restored during the infusion of BAY y 5959 but actually enhanced above pre–heart failure baseline levels. Thus, the calcium promoter was able to rapidly reverse the impaired baroreflex sensitivity in heart failure and permit the expression of the bradycardia in response to the drug, which as noted above appeared to be mediated by a central neural/vagal mechanism.

The next goal of the present investigation was to determine the mechanism of action of the drug on baroreflex sensitivity. It is conceivable that the calcium promoter affected the arterial baroreflex directly at the site of receptors in the carotid sinus and aortic arch or at the level of central neural integration. To address this question, low doses of the calcium promoter were infused to the brain through a chronically implanted internal carotid arterial catheter with the tip distal to the baroreceptors. In these experiments, when BAY y 5959 was infused to the brain and PI/SAP slopes were constructed during the infusion, the PI/SAP slope, ie, baroreflex sensitivity, was restored. As noted above, when these small quantities of drug were infused systemically, there was

PI/SAP slope significantly (12.7±2.8 ms/mm Hg, n=4, P<0.05) compared with the slope in heart failure in the absence of BAY y 5959 infusion (4.8±0.5 ms/mm Hg).

**Discussion**

Decreased baroreflex sensitivity is a hallmark of heart failure and has been associated with increased mortality.7 Decreased baroreflex sensitivity in heart failure was confirmed in the present study in the model of chronic rapid pacing by observation of blunted reflex bradycardia in response to norepinephrine-induced hypertension on the one hand and depressed PI/SAP slopes in response to pharmacological alterations in arterial pressure on the other hand.

In the present investigation, blunted inotropic responses to the catecholamine norepinephrine were observed, but the inotropic responses to the calcium promoter were preserved. In addition, the bradycardia induced by the calcium promoter was also not diminished in the presence of heart failure, in contrast to the blunted reflex bradycardia in response to norepinephrine. This catecholamine was selected for comparison because, like the calcium promoter, it increases myocardial contractility and arterial pressure while reducing the heart rate. Of course, the mechanism for the inotropic response differs for the 2 agents, as does the bradycardia.

The bradycardia in response to norepinephrine is mediated by the arterial baroreceptor reflex. The first goal of the present investigation was to determine the mechanism of the bradycardia in response to the calcium promoter. Because the bradycardia was completely abolished by ganglionic blockade, we concluded that the bradycardia was neurally mediated and not due to a direct effect of the drug. However, because the bradycardia was not abolished in the dogs with SAD, a baroreflex mechanism was not entirely responsible for the autonomously mediated bradycardia. These data, taken in combination, suggest that the bradycardia in response to the calcium promoter was mediated to a major extent by a central neural mechanism. Potentially, the drug could act to increase vagal nerve activity, a mechanism consistent with the findings that the bradycardia was abolished by ganglionic blockade but not by SAD. In further support of this concept, intra–carotid artery infusions of small quantities of BAY y 5959 elicited bradycardia without increasing arterial pressure. However, when the same dose of the drug was administered systemically, no effects on hemodynamics or heart rate were observed. Furthermore, in control dogs, the bradycardia was abolished with atropine, whereas in the presence of heart failure, a component of the bradycardia, presumably due to sympathetic withdrawal, persisted after muscarinic blockade. This suggests that a component of the efferent bradycardia in heart failure with the afferent loop in the central nervous system is mediated by sympathetic withdrawal. A parallel situation occurs with the arterial baroreflex control of heart rate, which is almost entirely vagal in the control state but includes a component of sympathetic withdrawal in heart failure.10

The fact that the calcium promoter elicited the same bradycardia in the presence and absence of heart failure implied that the well-known blunted arterial baroreflex sensitivity characteristic of heart failure was actually preserved during BAY y 5959 infusion. To confirm that depressed baroreflex sensitivity occurred in the model of pacing-induced heart failure,7 we examined PI/SAP slopes in response to pharmacologically induced hypotension and hypertension. As expected, the PI/SAP slopes were depressed in heart failure. Surprisingly, the PI/SAP slope, ie, baroreflex sensitivity, was not only restored during the infusion of BAY y 5959 but actually enhanced above pre–heart failure baseline levels. Thus, the calcium promoter was able to rapidly reverse the impaired baroreflex sensitivity in heart failure and permit the expression of the bradycardia in response to the drug, which as noted above appeared to be mediated by a central neural/vagal mechanism.

The next goal of the present investigation was to determine the mechanism of action of the drug on baroreflex sensitivity. It is conceivable that the calcium promoter affected the arterial baroreflex directly at the site of receptors in the carotid sinus and aortic arch or at the level of central neural integration. To address this question, low doses of the calcium promoter were infused to the brain through a chronically implanted internal carotid arterial catheter with the tip distal to the baroreceptors. In these experiments, when BAY y 5959 was infused to the brain and PI/SAP slopes were constructed during the infusion, the PI/SAP slope, ie, baroreflex sensitivity, was restored. As noted above, when these small quantities of drug were infused systemically, there was

**Figure 3.** Top, Examples of individual data; bottom, mean±SEM data. Depressed PI/SAP slope after IV nitroglycerin and phenylephrine is shown in heart failure (open bar). Slope was enhanced with intra–carotid artery infusion of BAY y 5959 (solid bar). However, when same dose of BAY y 5959 was administered systemically (shaded bar) in heart failure, slope was not affected, because dose was too low to be effective systemically.

In the present investigation, blunted inotropic responses to the catecholamine norepinephrine were observed, but the inotropic responses to the calcium promoter were preserved. In addition, the bradycardia induced by the calcium promoter was also not diminished in the presence of heart failure, in contrast to the blunted reflex bradycardia in response to norepinephrine. This catecholamine was selected for comparison because, like the calcium promoter, it increases myocardial contractility and arterial pressure while reducing the heart rate. Of course, the mechanism for the inotropic response differs for the 2 agents, as does the bradycardia.

The bradycardia in response to norepinephrine is mediated by the arterial baroreceptor reflex. The first goal of the present investigation was to determine the mechanism of the bradycardia in response to the calcium promoter. Because the bradycardia was completely abolished by ganglionic blockade, we concluded that the bradycardia was neurally mediated and not due to a direct effect of the drug. However, because the bradycardia was not abolished in the dogs with SAD, a baroreflex mechanism was not entirely responsible for the autonomously mediated bradycardia. These data, taken in combination, suggest that the bradycardia in response to the calcium promoter was mediated to a major extent by a central neural mechanism. Potentially, the drug could act to increase vagal nerve activity, a mechanism consistent with the findings that the bradycardia was abolished by ganglionic blockade but not by SAD. In further support of this concept, intra–carotid artery infusions of small quantities of BAY y 5959 elicited bradycardia without increasing arterial pressure. However, when the same dose of the drug was administered systemically, no effects on hemodynamics or heart rate were observed. Furthermore, in control dogs, the bradycardia was abolished with atropine, whereas in the presence of heart failure, a component of the bradycardia, presumably due to sympathetic withdrawal, persisted after muscarinic blockade. This suggests that a component of the efferent bradycardia in heart failure with the afferent loop in the central nervous system is mediated by sympathetic withdrawal. A parallel situation occurs with the arterial baroreflex control of heart rate, which is almost entirely vagal in the control state but includes a component of sympathetic withdrawal in heart failure.10

The fact that the calcium promoter elicited the same bradycardia in the presence and absence of heart failure implied that the well-known blunted arterial baroreflex sensitivity characteristic of heart failure was actually preserved during BAY y 5959 infusion. To confirm that depressed baroreflex sensitivity occurred in the model of pacing-induced heart failure,7 we examined PI/SAP slopes in response to pharmacologically induced hypotension and hypertension. As expected, the PI/SAP slopes were depressed in heart failure. Surprisingly, the PI/SAP slope, ie, baroreflex sensitivity, was not only restored during the infusion of BAY y 5959 but actually enhanced above pre–heart failure baseline levels. Thus, the calcium promoter was able to rapidly reverse the impaired baroreflex sensitivity in heart failure and permit the expression of the bradycardia in response to the drug, which as noted above appeared to be mediated by a central neural/vagal mechanism.

The next goal of the present investigation was to determine the mechanism of action of the drug on baroreflex sensitivity. It is conceivable that the calcium promoter affected the arterial baroreflex directly at the site of receptors in the carotid sinus and aortic arch or at the level of central neural integration. To address this question, low doses of the calcium promoter were infused to the brain through a chronically implanted internal carotid arterial catheter with the tip distal to the baroreceptors. In these experiments, when BAY y 5959 was infused to the brain and PI/SAP slopes were constructed during the infusion, the PI/SAP slope, ie, baroreflex sensitivity, was restored. As noted above, when these small quantities of drug were infused systemically, there was
no effect. Thus, it was the central neural effect of the calcium promoter that was able to restore baroreflex sensitivity in the presence of heart failure. The results from other studies with central nervous system injection of either calcium, calcium agonists, or dihydropyridine derivatives have been controversial; ie, both increasing and decreasing calcium has been shown to result in bradycardia.9–22

In summary, the calcium promoter BAY y 5959 elicits autonomously mediated bradycardia through the central nervous system rather than through the arterial baroreceptor reflex. Importantly, this action is preserved in heart failure. The calcium promoter not only restores but also enhances baroreflex sensitivity in heart failure above the control, pre–heart failure levels. These actions, in addition to the lack of desensitization of its inotropic effects, make this class of drugs important candidates to consider therapeutically in heart failure.

Acknowledgments

This study was supported in part by US Public Health Service grants HL-59139, HL-33107, HL-37404, and AG-14121; a gift from Bayer Pharmaceutical Co; and a Fellowship from Merck & Co, Inc.

References


Voltage-Dependent Calcium Channel Promoter Restores Baroreflex Sensitivity in Conscious Dogs With Heart Failure
Masami Uechi, Kuniya Asai, Naoki Sato and Stephen F. Vatner

Circulation. 1998;98:1342-1347
doi: 10.1161/01.CIR.98.13.1342

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1998 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/98/13/1342

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/