Sodium channel enhancer restores baroreflex sensitivity in conscious dogs with heart failure

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Shen, Weiqun, Robert M. Gill, Jian-Ping Zhang, Bonita D. Jones, Angela K. Corbly, and Mitchell I. Steinberg. Sodium channel enhancer restores baroreflex sensitivity in conscious dogs with heart failure. *Am J Physiol Heart Circ Physiol* 288: H1508–H1514, 2005. First published November 24, 2004; doi:10.1152/ajpheart.00337.2004.—We compared the cardiac inotropic, lusitropic, and chronotropic responses to the Na⁺ channel enhancer LY-368052 in conscious dogs before and after development of congestive heart failure (CHF). We also examined the effect of LY-368052 on baroreflex sensitivity and the efferent neural mechanisms of the bradycardic response in heart failure. Dogs were chronically instrumented, and heart failure was induced by right ventricular pacing at 240 beats/min for 3–4 wk. LY-368052 dose-dependently increased left ventricular contractile performance before and after the development of CHF to a similar extent. The inotropic effect of LY-368052 in heart failure was not altered by either ganglionic or β-adrenergic receptor blockade. LY-368052 improved cardiac relaxation and induced bradycardia in dogs with heart failure but not in normal dogs. The negative chronotropic effect of LY-368052 was eliminated by ganglionic blockade but not β-adrenergic blockade, suggesting that the bradycardia was mediated by the autonomic nervous system via enhanced parasympathetic tone. Baroreflex sensitivity was assessed as the pulse interval-mean arterial pressure slope in response to temporary pharmacological (nitroglycerin or phenylephrine) and mechanical (brief occlusion of inferior vena cava) alterations of arterial pressure in conscious dogs before and after development of heart failure. Baroreflex sensitivity was significantly depressed in heart failure and restored completely by acute treatment with LY-368052. Thus the Na⁺ channel enhancer LY-368052 maintains its β-receptor-independent inotropic effect in chronic CHF and specifically improves ventricular relaxation and depressed baroreflex function.

Bradycardia; cardiac inotropic response

**BAROREFLEX IMPAIRMENT** is a prominent characteristic of the heart failure syndrome (5, 12, 23, 38). Blunted baroreflex sensitivity and reduced heart rate variability directly contribute to the morbidity of chronic heart failure as well as to acute coronary events (1, 35); thus preserving baroreflex sensitivity in heart failure should be clinically relevant. Impaired Na⁺ and Ca²⁺ regulation has been suggested to mediate alterations of baroreflex function (18), and a voltage-dependent Ca²⁺ channel promoter was reported recently to restore baroreflex sensitivity in heart failure (36).

Synthetic Na⁺ channel enhancers have been proposed as a novel class of cardiac positive inotropic agents (8, 9, 32). These agents prolong the open state of cardiac Na⁺ channels and secondarily enhance reverse-mode Na⁺/Ca²⁺ exchange, resulting in an increase of intracellular free Ca²⁺ (25–27). Their cardiac positive inotropic effects have been demonstrated repeatedly in vitro (6, 10, 21, 25) as well as in vivo (3, 11, 30, 34). Our recent study (30) in conscious dogs with pacing-induced heart failure demonstrated that the Na⁺ channel enhancer LY-341311 not only increased cardiac contractile performance but also produced a prominent neurally mediated bradycardia in dogs with heart failure, indicating an improved balance between sympathetic and parasympathetic regulation. Thus we hypothesized that the enhancement of Na⁺ channel opening and the secondary increase of cellular Ca²⁺ could positively improve impaired baroreflex function in conscious dogs with pacing-induced heart failure.

The primary goal in the present study was to assess specifically the impact of augmented Na⁺ channel opening on baroreflex sensitivity in heart failure by assessing the baroreflex response during reflex tachycardia in response to temporary pharmacological and mechanical alterations of arterial pressure. We selected the Na⁺ channel enhancer R-4-[3-[(1-(diphenylmethyl)-3-azetidinyl)oxy]-2-hydroxypropylamino]-1H-indole-2-carbonitrile-3-mandelate (LY-368052) for study because it is a close structural analog of LY-341311, which was previously studied, but is ~10 times more potent (19, 32). The secondary goal in the study was to reveal the possible efferent neural mechanisms during the cardiac chronotropic responses to the Na⁺ channel enhancer by examining the bradycardic effect of LY-368052 in the presence and absence of ganglionic blockade with hexamethonium or β-adrenergic receptor blockade with propranolol. In addition, we compared the cardiac inotropic and lusitropic responses to the Na⁺ channel enhancer before and after the development of heart failure to ascertain the extent to which this agent retains its hemodynamic effects in the presence of congestive heart failure (CHF).

**METHODS**

**Animal and Surgical Preparation**

Male adult mongrel dogs (20–30 kg) were anesthetized with isoflurane in oxygen and ventilated with a respirator after induction with acepromazine (0.03 mg/kg im) and propofol (5.5 mg/kg iv). A left thoracotomy was performed through the fifth intercostal space under sterile technique. Tygon catheters were implanted in the descending thoracic aorta, left atrial appendage, and left ventricle (LV) for measuring pressures. A solid-state miniature pressure transducer (model P6; Konigsberg, Pasadena, CA) was placed into the LV chamber via an apical stab incision for recording LV pressure (LVP).

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A pair of piezoelectric ultrasonic crystals was placed on opposing anterior and posterior endocardial surfaces of the LV for measuring LV internal diameter (LVID). A screw-in pacing lead was attached to the right ventricular free wall, and stainless steel pacing wires were placed on the left atrium. An occluder was placed on the inferior vena cava (IVC). All instruments were secured with sutures. The catheters and lead wires were externalized, the thoracotomy was closed in layers, and the intrapleural space was evacuated. Cephalexin (500 mg) was administered postoperatively for 7 days after surgery. Control experiments were initiated 2–3 wk after surgery when the dogs were healthy, i.e., body temperature, blood cell count, and chemistry were within normal limits. The study was approved by the Lilly Institutional Animal Care and Use Committee, and all animals were maintained in accordance with the guidelines in the Guide for Care and Use of Laboratory Animals [DHHS Pub. No.(NIH) 83-23, Revised 1985].

Canine Model of Chronic Heart Failure

After the initial control study, heart failure was induced by chronic rapid right ventricular pacing at 240 beats/min for 3–4 wk with a programmable pacemaker (model EV4543; Pace Medical, Waltham, MA) that was worn externally in a vest.

Measurements and Data Analysis

Dogs were studied in the conscious state while lying quietly on their right side. Hemodynamic measurements were recorded in sinus rhythm after a 20- to 30-min stabilization period after the pacemaker was turned off. All signals were collected online and analyzed on a beat-to-beat basis with a digital data acquisition system (Ponemah; Gould Instrument System). The sampling rate was 250 Hz for arterial pressure (AP) and left atrial pressure (LAP) and 500 Hz for LV pressure and LVID. AP and LAP were measured with strain gauge transducers (P23 ID; Gould Statham, Valley View, OH) previously calibrated by a mercury manometer and connected to the fluid-filled aortic and left atrial catheters. LVP was measured with a solid-state miniaturized pressure gauge and calibrated in vivo against the measurement of AP and LAP. The first derivative of LV pressure (LV dP/dt) and maximum LV dP/dt (LV dp/dt max) were computed online by computer. LVID was measured with an ultrasonic transit time diameter gauge (Crystal Biotech, Houston, TX). LV shortening was calculated as LV end-diastolic internal diameter (LVEDD) – LV end-systolic internal diameter (LVESD), and LV fractional shortening (LVFS, %) was calculated as 100 × (LVEDD – LVEDD)/LVESSD. The mean velocity of circumferential fiber shortening (Vcfc, s−1) corrected for heart rate (HR) was calculated as [(LVEDD – LVESSD)/LVESSD]/[LV ejection time/(R-R interval)1/2]. LV stroke work was measured as the integral area of the pressure-diameter loops, and LV minute work was calculated as LV stroke work × HR (30, 33). The position of all catheters and crystals was confirmed after death. In addition, a lead II electrocardiogram was also recorded, and PR interval, QRS duration, and QT interval were measured. The corrected QT interval (QTc interval) was computed as the QT interval divided by the square root of the R-R interval in seconds.

Experimental Protocols

Cardiac effect of LY-368052 before and after heart failure. The effects of LY-368052 on hemodynamics and cardiac function were compared in seven dogs before and after development of pacing-induced heart failure. In this study, LY-368052 was administered as a 15-min graded intravenous infusion of 2, 5, 10, and 20 μg·kg−1·min−1. The dose and infusion time were selected on the basis of preliminary studies confirming that steady-state responses were achieved with this dosing protocol. Hemodynamic and cardiac functional data were recorded throughout the experiment. Effect of LY-368052 with ganglionic blockade or β-adrenergic blockade. The hemodynamic and cardiac responses to LY-368052 were also examined after pretreatment with ganglionic blockade. A single dose of LY-368052 (10 μg·kg−1·min−1) was administered by intravenous infusion for 20 min with or without ganglionic blockade induced by either hexamethonium alone (30 mg/kg iv; n = 4) or the combination of hexamethonium (30 mg/kg iv) and atropine methyl bromide (0.1 mg/kg iv) (n = 5). The effect of LY-368052 (10 μg·kg−1·min−1 for 20 min) on cardiac contractile function and hemodynamics was also examined in the absence and presence of β-adrenergic receptor blockade with propranolol (0.5 mg/kg iv). The β-adrenergic blocking effect of propranolol was confirmed by bolus intravenous injections of isoproterenol (0.1 and 0.25 μg/kg) before and after β-adrenergic blockade.

Effect of LY-368052 on baroreflex sensitivity. Baroreflex sensitivity was assessed as the pulse interval-mean arterial pressure (PI/MAP) slopes in conscious dogs before and after pacing-induced heart failure. The PI/MAP slopes were analyzed by linear regression for the reflex tachycardia response (R-R interval) to the temporary alteration of MAP induced by administration of nitroglycerin (20–50 μg/kg iv; n = 9) or phenylephrine (20–50 μg/kg iv; n = 8) by temporary inflation of a preimplanted IVC occluder (n = 5). Baroreflex sensitivity was determined before and after infusion of LY-368052 (10 μg·kg−1·min−1 iv for 20 min) in dogs with heart failure. The effect of LY-368052 on electrocardiogram parameters was also evaluated at the same time.

Materials

LY-368052 was dissolved (1 mg/ml) in a stock solution containing 1% (vol/vol) glacial acetic acid, 2% (vol/vol) absolute ethanol, 2.5% (wt/vol) L-ascorbic acid, and distilled water to volume. Stock solution was diluted in 0.9% NaCl for intravenous dosing. Hexamethonium, atropine methyl bromide, and phenylephrine (all from Sigma, St. Louis, MO) and nitroglycerin (Abbott Laboratories, Chicago, IL), were diluted directly in 0.9% NaCl saline solution.

Statistical Analysis

For hemodynamic and cardiac function, data are expressed as means ± SE, and a one-way factorial ANOVA was used to determine overall significance of differences. If the ANOVA demonstrated significant overall differences, individual comparisons between baseline and the response to each drug were made by contrast analysis. Regression analysis was used to determine the slope of baroreflex sensitivity, and statistical significance was determined by t-test. All changes were considered significant at P < 0.05 with a two-tailed t distribution.

RESULTS

Hemodynamics and LV Function Before and After Development of Heart Failure

Hemodynamics and LV function were measured in the conscious state, and heart failure was induced by chronic cardiac pacing. Compared with prepping baseline, there were significant decreases in MAP, LV dP/dt max, LVFS, Vcfc, minimum LV dp/dt (LV dp/dt min), LV stroke work, and minute work accompanied by increases in LAP, LVEDP, relaxation time constant (τ), and HR after 3–4 wk of rapid ventricular pacing (Table 1). Exsional dyspnea and ascites were also observed. All hemodynamic and cardiac functional data and clinical signs indicated the development of severe CHF by cardiac pacing, consistent with previous studies (29, 30, 31).
Inotropic, Lusitropic and Bradycardic Effects of LY-368052 in Absence or Presence of CHF

Inotropic, lusitropic, and bradycardic effects of the Na+ channel enhancer were examined in seven dogs before and after the development of heart failure induced by cardiac pacing. LY-368052 caused an insignificant change in HR in normal dogs (pre-pacing) but a marked bradycardic response (−26 ± 8%; P < 0.05) in heart failure (Table 1, Fig. 1).

LY-368052 (2−20 μg·kg⁻¹·min⁻¹) resulted in a dose-dependent increase in cardiac contractile performance in both the control state and heart failure (Table 1, Figs. 1 and 2). Compared with prepacing, LY-368052 (20 μg·kg⁻¹·min⁻¹) caused a similar increase in LV dP/dt max (137 ± 32% vs. 123 ± 25%) in heart failure. However, without a significant change in LVEDD, LY-368052 resulted in a greater increase in LVFS (117 ± 35% vs. 29 ± 8%; P < 0.05) and in LV V ecf (158 ± 46% vs. 41 ± 9%; P < 0.05) and was accompanied by a longer LV ejection time (2 ± 3% vs. −14 ± 2%; P < 0.05). Thus compared with control, LY-368052 markedly increased both LV stroke work (206 ± 61% vs. 47 ± 13%; P < 0.05) and LV minute work (123 ± 43% vs. 65 ± 18%) in heart failure (Figs. 1 and 2, Table 1). These data therefore clearly demonstrate that the positive cardiac inotropic effect of LY-368052 is preserved in conscious dogs with heart failure.

LY-368052 did not significantly alter LV dP/dt min and relaxation τ in normal dogs (pre-pacing) but caused a significant increase in LV dP/dt min by 40 ± 6% (P < 0.05) and reduction of LV relaxation τ by 28 ± 6% (P < 0.05) in dogs with heart failure (Table 1, Fig. 3), demonstrating an improvement in LV diastolic relaxation.

Inotropic and Bradycardic Effect of LY-368052 in Dogs with Heart Failure in Presence of β-Adrenergic Receptor or Ganglionic Blockade

The inotropic and bradycardic effects of LY-368052 were examined in conscious dogs with heart failure before and after β-adrenergic receptor blockade with propranolol. Compared with baseline, pretreatment with propranolol resulted in a significant decrease in LV dP/dt max by 27 ± 3%, without a significant change in HR. β-Adrenergic receptor blockade was confirmed by the complete inhibition of the response to isoproterenol (Fig. 4, left). LY-368052 increased LV dP/dt max and

Table 1. Effects of LY-368052 (20 μg·kg⁻¹·min⁻¹) on hemodynamics and LV function in conscious dogs before and after development of heart failure

<table>
<thead>
<tr>
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<th>Control</th>
<th>CHF</th>
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<tr>
<td></td>
<td>Baseline</td>
<td>% change</td>
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<tr>
<td>Heart rate, bpm</td>
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<tr>
<td>Mean arterial pressure, mmHg</td>
<td>82 ± 5</td>
<td>7 ± 8</td>
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<tr>
<td>Left atrial pressure, mmHg</td>
<td>103 ± 3</td>
<td>5 ± 5</td>
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<tr>
<td>LV end-diastolic pressure, mmHg</td>
<td>4 ± 1</td>
<td>−12 ± 20</td>
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<tr>
<td>LV systolic pressure, mmHg</td>
<td>8 ± 1</td>
<td>−12 ± 10</td>
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<tr>
<td>LV dP/dt max, mmHg/s</td>
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<tr>
<td>LV end-diastolic diameter, mm</td>
<td>3,124 ± 155</td>
<td>123 ± 25*</td>
</tr>
<tr>
<td>LV fractional shortening, %</td>
<td>34.9 ± 2.3</td>
<td>−2.5 ± 1.1*</td>
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<tr>
<td>LV V ecf, s⁻¹</td>
<td>1.09 ± 0.03</td>
<td>41 ± 9*</td>
</tr>
<tr>
<td>LV ejection time, ms</td>
<td>191 ± 5</td>
<td>−14 ± 2*</td>
</tr>
<tr>
<td>LV dP/dt max, mmHg/s</td>
<td>2,749 ± 76</td>
<td>−2 ± 5</td>
</tr>
<tr>
<td>LV relaxation τ, s⁻¹</td>
<td>24.2 ± 1.05</td>
<td>2 ± 12</td>
</tr>
<tr>
<td>Stroke work, dyn·cm⁻¹·min⁻¹·10³</td>
<td>146 ± 12</td>
<td>47 ± 13*</td>
</tr>
<tr>
<td>Cardiac work, dyn·cm⁻¹·min⁻¹·10⁶</td>
<td>11.9 ± 1.1</td>
<td>65 ± 18*</td>
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Data are means ± SE; n: number of animals; LV, left ventricle; LV dP/dt max, LV dP/dt min maximum and minimum first derivative of LV pressure; V ecf, velocity of circumferential fiber shortening; τ, time constant; bpm, beats per minute. *P < 0.05 vs. baseline; †P < 0.05 vs. control (preparing).
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LY-368052 also caused a dose-dependent bradycardic effect in heart failure, consistent with our previous findings with the less potent analog LY-343131 (30). The specific bradycardic effect accompanying the positive cardiac inotropic response in heart failure is characteristic for Na\(^+\) channel enhancers and distinguishes them from catecholamines, such as dobutamine, which are often associated with tachycardia. The bradycardic effect of the Na\(^+\) channel enhancer was eliminated after ganglionic blockade, indicating that the reduction of HR was mainly mediated by the autonomic nervous system. The bradycardic effect of LY-368052 was completely preserved in the presence of \(\beta\)-adrenergic blockade, demonstrating that the reduction of HR was mediated by increased parasympathetic activity and not due to changes in sympathetic outflow. Interestingly, the bradycardic effect with LY-368052 occurred only experimental and clinical settings (5, 23). Consistent with previous observations (36, 38), depressed baroreflex sensitivity was demonstrated in the present study by blunted reflex change of HR in response to pharmacological and mechanical alterations of arterial pressure in conscious dogs with pacing-induced heart failure. The most important finding in our study was that the depressed PI/MAP slopes in response to either pharmacological or mechanical alteration of arterial pressure in heart failure were restored completely to pre-heart failure levels after acute treatment with the Na\(^+\) channel enhancer.

Alteration of Baroreflex Sensitivity by LY-368052

Baroreflex sensitivity was evaluated as the PI/MAP slopes constructed for the HR response to temporary reflex change of blood pressure induced by phenylephrine, nitroglycerin, or IVC occlusion. Compared with the pre-heart failure response, the PI/MAP slopes obtained with phenylephrine (13.6 ± 2.4 vs. 6.1 ± 1.5 ms/mmHg; \(P < 0.05\)), nitroglycerin (7.6 ± 0.7 vs. 3.0 ± 0.5 ms/mmHg; \(P < 0.05\)) and IVC occlusion (7.4 ± 1.3 vs. 1.5 ± 1.7 ms/mmHg; \(P < 0.05\)) were all significantly reduced after the development of heart failure. Treatment of heart failure animals with LY-368052 (10 \(\mu\)g·kg\(^{-1}\)·min\(^{-1}\) for 20 min) completely restored the PI/MAP slopes to the control level under each experimental condition (Fig. 6), indicating an acute and specific restoration of baroreflex sensitivity by LY-368052 in heart failure.

Effects of LY-368052 on Electrocardiographic Parameters

The possible impact of Na\(^+\) channel enhancers on electrocardiographic parameters in dogs with heart failure was examined in the conscious state. LY-368052 caused a significant decrease in heart rate, resulting in increased PR and QT intervals; however, there was no change in QRS duration or QTc interval (Table 2).

**DISCUSSION**

Decreased baroreflex sensitivity is a hallmark of heart failure and is associated with increased mortality and morbidity in decreased HR to the same extent in the absence and presence of propranolol (1,110 ± 326 vs. 1,349 ± 154 mmHg/s and \(-43 ± 10\) vs. \(-44 ± 8\) beats/min, respectively; Fig. 4, middle and right). The cardiac inotropic and bradycardic effects of LY-368052 were also examined before and after pretreatment with ganglionic blockade. Although the inotropic effect of LY-368052 was unaltered by inhibiting central autonomic outflow to the heart by hexamethonium alone or combined with atropine, its bradycardic effect was nearly abolished (Fig. 5). Thus, in conscious dogs, LY-368052 directly enhances contractility by a \(\beta\)-adrenergic receptor-independent mechanism, but its bradycardic activity is dependent on intact autonomic pathways via an enhancement of parasympathetic tone.

Fig. 2. Dose-dependent effects of LY-368052 on LV stroke work and LV minute work in conscious dogs (\(n = 7\)) before (control) and after development of CHF. All data are means ± SE. *\(P < 0.05\) vs. prepacing control.

Fig. 3. Dose-dependent effects of LY-368052 on minimum first derivative of LV pressure (LV \(dP/dt_{\text{max}}\)) and LV relaxation time constant (\(\tau\)) in conscious dogs (\(n = 7\)) before (control) and after development of CHF. All data are means ± SE. *\(P < 0.05\) vs. prepacing control.
in dogs with heart failure and not in normal dogs. Because vagal withdrawal is a major component of the tachycardia of heart failure (15), this observation suggests that the Na\(^+\)/H\(^+\) channel enhancer specifically corrects the high sympathetic and low parasympathetic tone imbalance in heart failure.

It remains unclear whether the bradycardic effect results from the recovery of baroreflex sensitivity induced by the Na\(^+\) channel enhancer. However, depressed baroreflex control of HR has been suggested as one of the major mechanisms contributing to the elevated sympathetic tone and depressed vagal activity in heart failure (37, 39). Thus rapid restoration of the depressed baroreflex sensitivity and the rebalancing of sympathetic and vagal tone in heart failure with LY-368052 could lead to an autonomically mediated reduction in HR. However, it is worth noting that the Ca\(^{2+}\) channel promoter BAY y 5959 resulted in bradycardia through a direct central effect that was independent of enhanced baroreflex sensitivity (36). Regardless of the precise mechanisms, our data clearly demonstrate that the Na\(^+\) channel enhancer was able to rapidly restore impaired...
baroreflex sensitivity and permit expression of a negative chronotropic response in heart failure. The combination of bradycardia and positive inotropy produces direct benefit for myocardial energy consumption, especially in the failing heart, because HR is a critical factor contributing to cardiac energy consumption. We showed previously (30) that LY-341311 caused little change in oxygen consumption during its inotropic response in conscious dogs with heart failure, unless the bradycardic effect of the agent was prevented by atrial pacing.

The preservation of the bradycardic response in heart failure also contributes to the cardiac inotropic response to Na\(^+\) channel enhancement in heart failure. As expected, LV end-diastolic volume, estimated from LVEDD, did not significantly change with LY-368052 even though HR decreased (Table 1), an observation consistent with the exhaustion of the Frank-Starling mechanism in canine heart failure (17). However, with a slower HR, LV ejection time becomes longer, allowing LV contraction to be more complete during the ejection phase as evidenced as a greater change in LVFS (Fig. 1). Consequently, the Na\(^+\) channel enhancer produced larger increases in LV stroke work and LV minute work in heart failure than in control animals.

Catecholamines are used clinically to improve the depressed LV function of heart failure, especially during acute decompensation. However, desensitization due to down-regulation of \(\beta\)-adrenergic receptor and cAMP pathway limits the efficacy of these agents in the therapy of advanced heart failure (7, 16). For example, the cardiac positive inotropic responses to dobutamine, as reflected by LV systolic pressure, LV dp/dr, and LVFS, were reduced by 65\% after the development of heart failure (2, 16). The cardiac inotropic responses to LY-368052 in dogs before and after development of heart failure were not different, suggesting that the Na\(^+\) channel enhancer may be devoid of desensitization in heart failure. In the current study, LY-368052 significantly increased myocardial contractile performance to the same extent in the presence and the absence of \(\beta\)-adrenergic receptor blockade, indicating that the positive inotropic response is \(\beta\)-adrenergic independent, consistent with earlier in vitro findings with these agents (24, 28).

Of particular interest was the finding that in CHF LV diastolic relaxation, as reflected by an increase in LV dp/dt\(_{\min}\) by 40 \(\pm\) 6\% and a reduction of LV \(\tau\) by 28 \(\pm\) 6\%, but caused little change in normal dogs. This was consistent with earlier findings with the less potent analog LY-341311 (13). Thus Na\(^+\) channel enhancers appear to exert not only positive inotropic but also positive lusitropic effects in heart failure. Because Na\(^+\) channel enhancers indirectly increase intracellular Ca\(^{2+}\) availability, this intracellular Ca\(^{2+}\) gain might have been expected to slow sarcoplasmic reticulum (SR) Ca\(^{2+}\) uptake and have an adverse effect on cardiac diastolic function. The mechanism(s) for the positive lusitropic effect in the failing heart is not known. It has been suggested, however, that a reduction of the Na\(^+\) gradient might also cause an increase in both Ca\(^{2+}\) influx and efflux; the latter being secondary to an enhanced release of Ca\(^{2+}\) from the SR (4). Clearly, additional work characterizing this effect at the cellular level is warranted.

Cardiac glycosides produce positive cardiac inotropic effect by increasing intracellular Na\(^+\) concentration through inhibition of the Na\(^+\)-K\(^+\)-ATPase. However, cardiac glycosides are well known to induce or aggravate arrhythmia (14). In the current study, LY-358052 did not significantly prolong the QRS duration or the QTc interval, although there was an increase in the QT interval that accompanied pacing-induced heart failure. These ECG interval data from conscious dogs with heart failure were consistent with earlier observations with a less potent Na\(^+\) channel enhancer (30). As in anesthetized dogs with infarction (3), we saw no overt arrhythmogenicity; nevertheless, our study was not specifically designed to address the arrhythmogenic potential of LY-368052, and further investigation in appropriate models seems warranted.

In summary, the Na\(^+\) channel enhancer LY-368052 restored impaired baroreflex sensitivity in CHF, thereby improving the balance between sympathetic and parasympathetic tone while maintaining potent \(\beta\)-adrenergic-independent inotropic effects. The enhanced myocardial efficiency of this agent compared with catecholamines may be useful in preventing further deterioration of myocardial energy stores in the setting of acute heart failure.

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