Hemodynamic Effects of a New Inotropic Compound, PST-2744, in Dogs With Chronic Ischemic Heart Failure

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Abstract: Inotropic agents for acute decompensated heart failure are associated with a lack of efficacy or increased mortality. New compounds are needed to support patients with acute exacerbations of heart failure. This study examined the hemodynamic effects of a new inotropic agent (PST-2744) in dogs with chronic ischemic heart failure. Eight mongrel dogs at low risk for postmyocardial infarction (MI) sudden death entered the protocol. Dogs were studied after ischemic left ventricular dysfunction was induced by repeated injections of latex microspheres into the circumflex artery until the ejection fraction reached 35%. Hemodynamic parameters were measured at baseline and peak drug effect (PST-2744 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$). In 5 animals, PST-2744 effects were compared with dobutamine. Heart rates, PR intervals and QT intervals were unchanged following PST-2744 administration. PST-2744 increased contractility (+dP/dt) by 56% from 1881 ± 282 mm Hg/s to 2939 ± 734 mm Hg/s ($P < 0.01$). The inotropic effect of PST-2744 was equal to that produced by 5-$\mu g \cdot kg^{-1} \cdot min^{-1}$ dobutamine (56% increase in +dP/dt), but peak heart rates were significantly higher with dobutamine (129 ± 24 bpm PST-2744 versus 160 ± 6 bpm 5-$\mu g \cdot kg^{-1} \cdot min^{-1}$ dobutamine, $P < 0.002$). No arrhythmias or conduction delays were seen with either compound. PST-2744 is an effective inotropic agent without positive chronotropic effect in subjects with stable moderate left ventricular dysfunction.

Key Words: congestive heart failure, ischemic heart disease, inotropic agents, dobutamine, hemodynamics

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Traditional therapy for acute decompensated heart failure often includes short-term infusion of positive inotropic agents to support the failing ventricle.[1–3] However, recent prospective data suggest that routine use of the phosphodiesterase inhibitor milrinone has no effect on short-term or intermediate-term hospital utilization. In fact, milrinone use increased atrial arrhythmias and caused sustained hypotension.[4] Chronic use of positive inotropic agents may improve symptoms, but intermittent administration of these compounds increase mortality risk.[5–9] Negative results of short-term infusions or increased mortality with chronic administration provides the impetus for development of new inotropic agents for acutely decompensated heart failure that do not possess the adverse side effects of currently available compounds.

A new positive inotropic compound under development, PST-2744, is a derivative of androstanedione chemically unrelated to cardiac glycosides or phosphodiesterase inhibitors, but able to inhibit the sodium/potassium ATPase pump.[10] Long-term administration of PST-2744 improves cardiac performance in a dose-dependent manner,[10] and appears to improve survival in cardiomyopathic hamsters.[11] Given the potential value of PST-2744 in acute decompensated heart failure, this study examined the hypothesis that PST-2744 administration acutely increases left ventricular (LV) contractility and analyzed the drug's effects on atrioventricular conduction, LV end-diastolic pressures, and potential for lethal arrhythmias. The study compared PST-2744 with dobutamine in a clinically applicable canine model of moderate ischemic LV dysfunction.[12]

METHODS

Animal Instrumentation and Production of Left Ventricular Dysfunction

The canine model of ischemic heart failure used in this study produced animals with moderate LV dysfunction (ejection fraction ~ 35%) as previously described.[12]

Mongrel dogs (2–4 years by dentition, 25 kg) were purchased and monitored for 2 weeks. After quarantine, each animal was instrumented with an anteroseptal myocardial infarction (MI) by permanent ligation of the left anterior descending

coronary artery through a left fifth interspace thoracotomy during surgical plane anesthesia. This procedure consistently creates an infarction that is 5% to 10% of the LV mass. The left circumflex coronary artery was dissected free from the epicardium and a pneumatic vascular occluder was placed around the artery to subsequently allow reversible ischemia in that distribution. A small catheter was implanted and secured in the lumen of the descending aorta to later measure blood pressure. Pacing leads were clipped to the right atrial appendage and the right ventricular free wall. All instrumentation was exteriorized by subcutaneous tunneling to the nape of the neck. Each animal received immediate postoperative short-term analgesia (pentazocine lactate, 1 mg/kg, IM) followed by a longer-acting analgesic (nalbuphine HCl, 0.5 mg/kg, IM). Guidelines outlined by the National Institutes of Health, American Physiological Society and the American Heart Association pertaining to the appropriate care and use of animals were strictly followed. All procedures were reviewed, approved, and supervised by the institutional animal care and use committee. Thirty days of recovery and acclimation to the facilities and personnel were allowed before any testing was started.

Risk for Ventricular Fibrillation After Myocardial Infarction

Thirty days after MI, each dog exercised in a submaximal stress test protocol previously published[13]. When target heart rate was reached (210–220 bpm), the circumflex occluder was inflated for 2 minutes; the animals continued to run during the first minute and exercise was stopped during the second minute. Dogs developing VF during the 2 minutes of myocardial ischemia lost consciousness and then were defibrillated. These animals were labeled "susceptible" or "high-risk" for VF. The remaining animals did not develop sustained ventricular arrhythmias and were labeled "resistant" or "low-risk" for VF. This protocol is associated with a >90% reproducibility of risk status.[13] Only resistant animals entered the present protocol.

Induction of Left Ventricular Dysfunction

One month after MI (5 ± 1 weeks), dogs were sedated with ACE promazine (1 mg/kg, SQ) and propofol (1 mg/kg IV) to effect. Dedicated personnel monitored the animal status and administered supplemental propofol when needed. Either the left or right superficial femoral artery was dissected using local anesthesia and sterile technique. A purse-string suture (4-0 silk) was placed in the media of the artery and an arteriotomy was made using an 18-gauge needle. Using a modified Seldinger technique, the femoral artery was cannulated with an introducer sheath over a wire (6F, Daig Corp.). Using a 6F Judkins 3.5 left diagnostic angiographic catheter (Medtronic, Inc.), the left main coronary artery was identified fluoroscopically. Angiographic contrast (Omnipaque) was used to identify and subselect the circumflex coronary artery. Sonicated and warmed latex microspheres (1–1.5 mL of 75–90 μm, Polysciences, Inc.) were then slowly injected into the artery carefully monitoring distal flow and runoff.

Electrocardiogram and arterial oxygen saturation were monitored throughout the procedure. When the embolization procedure was complete, the arteriotomy was closed with the purse string. Wound closure was accomplished using absorbable 2-0 suture (Vicryl) and skin staples were placed over the wound. Postoperative analgesia was induced using nalbuphine (0.5 mg/kg, IM). Dogs were continuously monitored until awake. This procedure was repeated weekly until the target ejection fraction was reached.

Echocardiography Evaluation

At baseline and 7 days after each embolization, the ejection fraction was measured using modified 2- and 4-chamber transthoracic echocardiogram views. The same investigator (P.B.A.) performed all echoes with care taken to maximize image acquisition. When ejection fraction reached 35%, another echocardiogram was obtained 7 days later to confirm LV dysfunction.

Drug Testing

After 8 ± 2 weeks of chronic stable LV dysfunction, dogs were sedated with diazepam (5 mg I.V. to effect with supplements as needed) after preanesthesia with ACE promazine. Using local anesthesia, the superficial femoral artery was cannulated using methods outlined previously. A fully calibrated Millar catheter was advanced across the aortic valve to a stable position in the left ventricle. Left ventricular systolic and diastolic pressures, LV +dP/dt and −dP/dt, ECG, and heart rate were digitally obtained (PowerLab 6) for 5 minutes and drug infusion was started. Infusions lasted 15 minutes each and, toward the end of the infusion, all parameters were measured. In the 5 dogs in which dobutamine and PST-2744 were tested, the animals were continuously monitored for 1 hour after stopping the infusion or until parameters returned to baseline values and, once this had occurred, the new infusion was started. Dobutamine was infused at 2.5 and 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. PST-2744 was infused at 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ to deliver 75 μg/kg total dose. This dose was chosen based on data from previous studies demonstrating maximal inotropic effect without proarrhythmia in dogs.[12] Dobutamine was always infused first and PST-2744 last with washout before the next drug was tested. Comparison with of all hemodynamic parameters and derivatives in the 3 animals in which dobutamine was not tested indicated that previous administration of dobutamine did not influence the effects of PST-2744.

Surface ECG Measurements

Surface QT intervals were measured immediately before and during drug testing. Qt intervals were corrected to the prevailing heart rate using the Bazett's formula. PR interval mea-

surements were made before and after drug infusion and the incidence of ventricular arrhythmias was also evaluated.

Statistical Analyses

Hemodynamic parameters were compared between baseline (no drug), PST-2744 and dobutamine (2.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and 5 μg/kg/min) using ANOVA for repeated measures. Different groups of observations were examined using a Tukey test. An α level of $P < 0.05$ was considered significant. Results are mean ± SD unless otherwise noted.

RESULTS

Production of Left Ventricular Dysfunction

Eight dogs entered the study after repeated microembolizations produced a resting ejection fraction of 34% ± 3%. The animals required a total of 6 ± 3 embolization sessions to produce the target ejection fraction.

Inotropic Effects of PST-2744

PST-2744 increased LV +dP/dt by 56.2% from 1882 ± 305 mm Hg/s to 2939 ± 793 mm Hg/s ($P < 0.04$). The magnitude of –dP/dt was not different (from −1597 ± 413 mm Hg/s to −1917 ± 525 mm Hg/s; P = NS, Fig. 1). The increased contractility with PST-2744 was not associated with a positive chronotropic effect when compared with baseline resting heart rates (132 ± 17 bpm baseline versus 129±24 bpm post PST-2744, P = NS). Left ventricular end-systolic pressures increased from 118 ± 15 mm Hg to 138 ± 18 mm Hg ($P < 0.03$, Fig. 2), but LV end-diastolic pressures were not different at the peak effect of PST-2744 (from 22 ± 11 mm Hg to 28 ± 10 mm Hg, P = NS). At peak effect, the compound did not change any

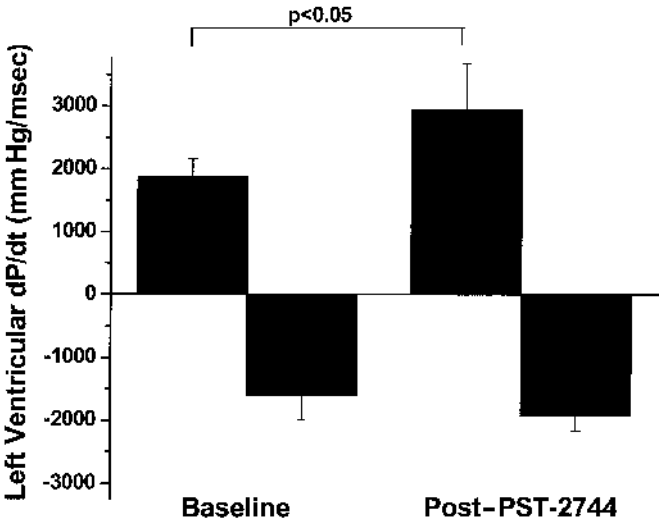

FIGURE 1. The dP/dt maximum and minimum before and after administration of PST-2744 (5-$\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion for 15 minutes).

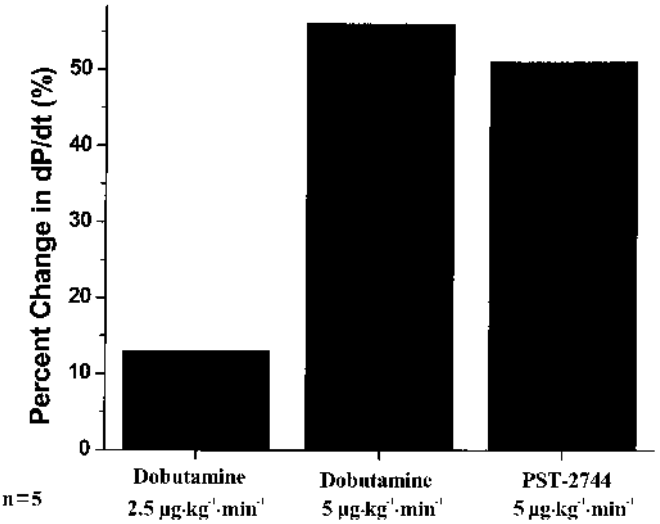

FIGURE 2. Change in dP/dt maximum comparing dobutamine at 2 doses to PST-2744. No difference was found between PST-2744 and 5-$\mu g \cdot kg^{-1} \cdot min^{-1}$ dobutamine, and 2.5-$\mu g \cdot kg^{-1} \cdot min^{-1}$ dobutamine did not significantly change dP/dt max. Both 5-$\mu g \cdot kg^{-1} \cdot min^{-1}$ dobutamine and PST-2744 significantly increased dP/dt maximum ($P < 0.05$).

electrophysiologic parameter: QT interval from 248 ± 8 milliseconds to 246 ± 28 milliseconds (P = NS), corrected QT from 358 ± 27 milliseconds to 355 ± 46 milliseconds (P = NS), and the PR interval from 103 ± 9 milliseconds to 107 ± 11 milliseconds peak (P = NS). No atrial or ventricular arrhythmias were noted during or after the infusion of PST-2744.

PST-2744 Versus Dobutamine

Comparison of PST-2744 to dobutamine was completed in 5 animals with depressed LV function. In these 5 animals, PST-2744 increased +dP/dt by 51% (from 1749 ± 182 mm Hg/s to 2633 ± 586 mm Hg/s, $P < 0.05$), which was equivalent to the effect of 5-$\mu g \cdot kg^{-1} \cdot min^{-1}$ dobutamine (from 1658 ± 297 mm Hg/s to 2592 ± 1353 mm Hg/s, +56%, P = NS, comparing PST-2744 to 5-$\mu g \cdot kg^{-1} \cdot min^{-1}$ dobutamine). The peak heart rate after dobutamine was higher than after PST-2744 (160 ± 6 bpm 5-$\mu g \cdot kg^{-1} \cdot min^{-1}$ dobutamine versus 120 ± 15 bpm PST-2744, $P < 0.002$).

Left ventricular end-diastolic pressures were not different after dobutamine (from 25 ± 10 mm Hg to 31 ± 9 mm Hg, P = NS) or PST-2744 therapy. Negative dP/dt max, a marker of relaxation, was unchanged after dobutamine therapy (from −1284± −475 mm Hg/s to −1516 ± −735 mm Hg/s, P = NS). Surface QT and PR intervals were not changed after dobutamine therapy. Lower doses of dobutamine (2.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) did not significantly change +dP/dt (from 1662 ± 299 mm Hg/s to 1887 ± 426 mm Hg/s, P = NS).

DISCUSSION

This study demonstrates that the novel inotropic agent, PST-2744, increases LV contractility in the failing ventricle,

resulting in significant increases in systolic pressure development without increases in preload (LVEDP) or heart rate. Although part of the pharmacologic effect of PST-2744 involves action on the same target as ouabain (the sodium/potassium ATPase pump), there was no significant effect of the compound on atrioventricular conduction or ventricular repolarization. No atrial or ventricular arrhythmias were seen during acute administration of PST-2744. These data suggest that the drug may be a safe means to provide acute inotropic support the failing ventricle without evidence for conduction abnormalities or ventricular arrhythmias.

Inotropic Action of PST-2744 Versus Dobutamine

The inotropic effect of PST-2744 in dogs with heart failure was equal to the β-agonist dobutamine, which is commonly used in clinical medicine to provide acute short-term support to the failing ventricle.[1,3] However, PST-2744 provided this support without affecting heart rate, which would lower oxygen consumption compared with dobutamine. Since most heart failure patients have ischemic heart disease, the role of heart rate during acute or chronic therapy is very important. Additionally, the growing use of β-blocker therapy in heart failure patients creates the need for new agents that do not act through β-adrenergic receptor activation. In this regard, long-term use of digoxin in patients with heart failure improves quality of life and decreases the need for hospitalizations, but the arrhythmogenic profile of cardiac glycosides discourages use in acute decompensation of the syndrome.

Recent clinical trial results further underscore the need for new inotropic agents in heart failure. The OPTIME trial tested the hypothesis that routine use of phosphodiesterase therapy in patients hospitalized for heart failure exacerbations, but found no benefit in short-term mortality or length of hospital stay.[4] In fact, milrinone therapy was associated with an increase in atrial arrhythmias and hypotension,[4] which may have contributed to the trial's negative results. Lethal arrhythmias are also thought to be the mechanism for increased mortality associated with chronic inotropic therapy.[5,6] The observation that PST-2744 provided an increase in contractility equal to dobutamine, but without significant chronotropic effect, may have important clinical implications for longer-term therapy with the compound. Specific conclusions about the proarrhythmic effect, however, would be best made in the setting of longitudinal studies evaluating long-term therapy.

Model of Ischemic Heart Failure

Since chronic heart failure is often caused by ischemic heart disease,[10] a model of ischemic LV dysfunction may provide useful information about compounds intended for use in heart failure. The model of ischemic heart failure used in this study is founded on a post-MI sudden death model that provided extensive information about autonomic and electrophysiologic mechanisms of sudden death.[13–18] Two groups of dogs are produced with predictable risk for lethal arrhythmias once LV dysfunction develops.[12] High-risk dogs die suddenly of spontaneous ventricular arrhythmias shortly after development of LV dysfunction. Low-risk dogs are characterized by isolated spontaneous ventricular ectopy, but very low long-term risk for lethal arrhythmias.[12] In the low-risk dogs, PST-2744 did not increase heart rate or ventricular arrhythmias during short-term infusion, but the study was not designed to examine potential proarrhythmia during long-term exposure to PST-2744.

Study Limitations

This study examined the effects of PST-2744 on markers of contractility that are influenced by sedation and other factors that alter loading conditions, which may have influenced the results. The design, however, allowed time for equilibration following sedation, which served as the control conditions. Furthermore, PST-2744 and dobutamine were compared in the same conditions to minimize the effects of sedation on the conclusions. The lack of proarrhythmia during short-term infusion, although encouraging, does not predict the compound's impact on the long-term risk of sudden death.

CONCLUSIONS

PST-2744 is a new positive inotropic agent with an efficacy equal to dobutamine when administered intravenously. The increase in contractility observed in this model was not associated with increased heart rate, conduction abnormalities, or short-term proarrhythmia. These data provide evidence that this compound may be effective in patients with chronic heart failure.

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