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# Ranolazine, a novel anti-anginal agent, does not alter isosorbide dinitrate- or sildenafil-induced changes in blood pressure in conscious dogs

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**Abstract**

Effects of ranolazine on isosorbide dinitrate- and on sildenafil-induced changes in mean arterial pressure and heart rate were assessed in conscious dogs. Dogs ($n=7$) were chronically instrumented for measurements of mean arterial pressure and heart rate. Bolus intravenous injections of either isosorbide dinitrate (0.2 mg/kg) or sildenafil (0.5 mg/kg) caused biphasic changes in mean arterial pressure and heart rate: a transient (~20 s) decrease in mean arterial pressure and an increase in heart rate, followed by prolonged (10–15 min) decreases in mean arterial pressure by 11±1.6 and 11±2.2 mm Hg, respectively. Infusion of ranolazine alone (plasma concentrations=4 or 8 μM) for 10 min did not significantly affect mean arterial pressure and heart rate. The transient hypotension and tachycardia caused by isosorbide dinitrate were not altered by ranolazine. The sildenafil-induced transient tachycardia (Δ change: 114±10 beats/min) was significantly ($P<0.05$) blunted by either 4 (Δ change: 71±8 beats/min) or 8 (Δ change: 66±9 beats/min) μM ranolazine. However, the sildenafil-induced transient decrease in mean arterial pressure was not altered by ranolazine. During ranolazine infusion (4–5 or 8–10 μM), isosorbide dinitrate and sildenafil caused prolonged decreases in mean arterial pressure. These results indicate that except for a blunting of the transient tachycardia caused by sildenafil, ranolazine at concentrations up to 10 μM does not alter changes in mean arterial pressure and heart rate induced by either isosorbide dinitrate or sildenafil in conscious dogs.


*Keywords:* Ranolazine; Long-acting nitrate; Sildenafil; Blood pressure; Heart rate; Conscious dog

## 1. Introduction

Three classes of anti-anginal drugs-nitrates, β-adrenoceptor antagonists and calcium channel blockers — have been approved for the treatment of chronic angina in the United States (Pepine et al., 1998; Heidenreich et al., 1999; Gibbons et al., 2003). More recently, a novel anti-anginal drug, ranolazine has been approved by the US Food and Drug Administration for the treatment of patients with chronic angina in combination with the above-mentioned anti-anginal drugs. Results of clinical trials show that ranolazine reduces the frequency of anginal attacks and increases exercise capacity in patients with chronic angina (Pepine et al., 1999; Chaitman, 2004a; Chaitman et al., 2004b,c). Results of some early studies suggested that ranolazine may inhibit free fatty acid oxidation and increase oxidation of glucose and lactate; however, this action appears to require a relatively high concentration of ranolazine (MacInnes et al., 2003). Recent results indicate that ranolazine is an inhibitor of the late sodium channel current (late $I_{Na}$) in cardiac myocytes. Selective inhibition of late $I_{Na}$ relative to peak $I_{Na}$ by ranolazine reduces sodium entry into myocytes during the action potential plateau, thereby reducing $Na^+/Ca^+$ exchange and attenuating the effect of ischemia to cause elevation of the intracellular calcium concentration (Antzelevitch et al., 2004; Song et al., 2004; Shryock et al., 2004).

Long-acting nitrates such as isosorbide dinitrate have been used for the treatment of chronic angina for two decades (Kerins et al., 2001), and sildenafil has been used for the treatment of

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erectile dysfunction, often in patients with diabetes or heart disease, since 1998 (Jackson, 2004). Isosorbide dinitrate is a nitric oxide donor and sildenafil is a selective inhibitor of cGMP-specific phosphodiesterase type 5. Both isosorbide dinitrate and sildenafil can cause increases in cGMP that result in vasodilation. When isosorbide dinitrate and sildenafil are used concurrently, dramatic reductions in blood pressure are sometimes observed (Schwemmer et al., 2001; Yoo et al., 2002; Zoma et al., 2004).

In clinical practice, ranolazine could be used in combinations with long-acting nitrates and sildenafil. Therefore, it is important to identify the potential interactive effects of these drugs on blood pressure and heart rate. The goal of this study was, therefore, to characterize interactive effects of ranolazine with isosorbide dinitrate and with sildenafil on mean arterial pressure and heart rate in conscious dogs.

## 2. Materials and methods

Male mongrel dogs ($n=7$) weighing 23–27 kg were used in this study. The animal protocol was approved by the Institutional Animal Care and Use Committee of New York Medical College and conforms to the Guide for the Care and Use of Laboratory Animals by the United States National Institutes of Health.

### 2.1. Surgical procedures

Each dog was sedated with acepromazine (0.3 mg/kg, i.m.) and anesthetized with pentobarbital sodium (25 mg/kg, i.v.). The chest was scrubbed with a sterilizing soap and sterilized with iodine solution. The dog was intubated and artificially ventilated with room air. A thoracotomy was made in the fifth intercostal space. A Tygon catheter (Cardiovascular Instruments, Wakefield, MA) was inserted into the descending thoracic aorta for the measurement of blood pressure and for blood sampling. Briefly, a piece of descending thoracic aorta was partially clamped, and a small hole was made through the vessel using an 18-gauge needle. A catheter was inserted into the aorta through the hole and secured using a suture. The chest was closed in layers. The catheter was tunneled subcutaneously and externalized through the skin at the back of the dog's neck. The dogs were allowed to recover from the surgery for 10–14 days and were trained to lie quietly on the laboratory table.

### 2.2. Recording from chronically instrumented dogs

On the day of an experiment, a dog was brought to the laboratory and placed on its right side on the table. The previously implanted catheter was connected to a strain gauge transducer (P23 ID, Statham, Newark, NJ), and mean arterial pressure was derived using a 2 Hz low-pass filter. Heart rate was monitored from the pressure pulse interval using a cardiotachometer (Beckeman Instruments, Newark, NJ). Additional catheters were inserted into a peripheral vein in one front and one rear leg, and attached to infusion lines to administer drugs without disturbing the dog. The experiment began after mean arterial pressure and heart rate were stable (usually 20 to 30 min). Dogs lay undisturbed, either awake or asleep, during an experiment.

### 2.3. Experimental protocols

#### 2.3.1. Effects of isosorbide dinitrate or sildenafil on mean arterial pressure and heart rate

Three experiments were performed on three different days in each dog. On the first experimental day, a dog received a bolus intravenous injection of isosorbide dinitrate (0.2 mg/kg, 9–11 ml), followed by 3 ml saline to flush the catheter. Two and one-half hours after the injection of isosorbide dinitrate, sildenafil (0.5 mg/kg, 9–11 ml) was administered intravenously. The half-life of isosorbide dinitrate in the dog is 45 min, thus blood isosorbide dinitrate concentrations after 2.5 h would be about 1/10 of the concentration at time "0". Mean arterial pressure and heart rate were recorded continuously for 30 min following each administration of drug.

#### 2.3.2. Effects of isosorbide dinitrate or sildenafil on mean arterial pressure and heart rate during infusion of ranolazine at 4–5 or 8–10 μM

On the second experimental day, the dog received a bolus intravenous injection (in 30 s by hand) of ranolazine at a dose of 1.6 mg/kg, followed by a 30–40 min infusion of ranolazine at a rate of 90 μg/kg/min. This dose of ranolazine was used to achieve a predicted plasma ranolazine concentration of 5 μM. Ten minutes after initiation of the ranolazine infusion, the dog received a bolus intravenous injection of isosorbide dinitrate (0.2 mg/kg). Mean arterial pressure and heart rate were measured continuously for 30 min, and then ranolazine infusion was stopped. Two hours later, ranolazine was again administered as an intravenous injection, followed by a continuous 30–40 min infusion. Ten minutes after initiation of the ranolazine infusion, the dog received a bolus intravenous injection of sildenafil (0.5 mg/kg). Mean arterial pressure and heart rate were measured continuously for 30 min, and then the ranolazine infusion was stopped. At 10 min after initiation of the ranolazine infusion, and again at 30 min after the injection of isosorbide dinitrate or sildenafil (during ranolazine infusion), 6 ml of blood was taken from the aortic catheter for the measurement of the plasma ranolazine concentration.

On the third day, the protocol described for the second day was repeated, except that the dog received an intravenous injection of ranolazine at a dose of 3.2 mg/kg, followed by an infusion of ranolazine at a rate of 170 μg/kg/min for 30–40 min. This dose of ranolazine was used to achieve a predicted plasma ranolazine concentration of 10 μM.

### 2.4. Determination of plasma concentration of ranolazine

Arterial blood samples were subjected to centrifugation for 15 min at 3000 *g* at 4 °C and the plasma was collected. Plasma samples were sent to the Preclinical Development Department at CV Therapeutics for the measurement of ranolazine concentrations using standard Liquid Chromatography/Mass Spectrometer procedures.

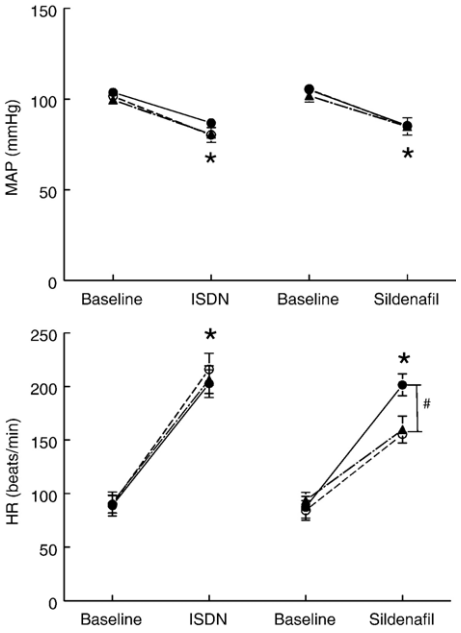


Fig. 1. Administrations of isosorbide dinitrate (ISDN) or sildenafil resulted in a transient decrease in mean arterial pressure (top panel) and a transient increase in heart rate (bottom). The transient increase in heart rate in response to sildenafil was significantly attenuated in the presence of 4–5 or 8–10 ranolazine, whereas the transient decrease in mean arterial pressure caused by sildenafil was not altered by ranolazine. Ranolazine at 4–5 or 8–10 μM did not alter isosorbide dinitrate-induced changes in mean arterial pressure and heart rate. Symbols ●, ○ and ▲ indicate absence, presence of 4–5 μM, and presence of 8–10 μM ranolazine, respectively. Values are mean±S.E.M, $n=6–7$, #$P<0.05$, compared to control group.

### 2.5. Drugs

Ranolazine was synthesized at CV Therapeutics, Inc. (Lot#: E4-NE-002). Isosorbide dinitrate (Westward, NJ, MW: 236.1) and sildenafil (Viagra®, Pfizer, NY, NY, MW: 666.7) were purchased from a local pharmacy.

Isosorbide dinitrate tablets (2.5 mg) were dissolved in 0.9% saline at a concentration of 0.5 mg/ml. Sildenafil in tablet form (50 mg) was crushed into a powder, added to 40 ml of 0.9% saline, and mixed well. The suspension was subjected to centrifugation at 3000 *g* for 20 min, and the supernatant was used for the intravenous injection (~1.25 mg/ml) (method described by Zoma et al., 2004).

### 2.6. Data analysis

Values of mean arterial pressure and heart rate before and after drug administration (at the peak response and at 5, 10, 15, 20, 25 and 30 min) were determined from the strip chart recording. Both the absolute change and the percentage change in mean arterial pressure and heart rate relative to control (before drug administration) were calculated in each experiment and used for statistical analysis. The statistical significance of a difference between mean arterial pressure and heart rate at control and at the indicated time points after drug administration was determined using a One-Way Repeated Measures Analysis of Variance (ANOVA), followed by Tukey's Test. Statistical significance of differences between responses to isosorbide dinitrate and to sildenafil in the absence and presence of ranolazine was determined using a Two-Way ANOVA followed by Tukey's Test. Differences associated with a probability ($P$)< 0.05 were considered to be significant. A computer-based software package (SigmaStat 2.03) was used for statistical analysis. All data are presented as mean±S.E.M.

## 3. Results

### 3.1. Effects of isosorbide dinitrate or sildenafil on mean arterial pressure and heart rate

A bolus intravenous injection of either isosorbide dinitrate (0.2 mg/kg) or sildenafil (0.5 mg/kg) caused a transient decrease in mean arterial pressure and a transient increase in heart rate lasting about 30 s, followed by a prolonged decrease in mean arterial pressure without a change in heart rate (Figs. 1–3). At the peak of the transient response, isosorbide dinitrate or sildenafil caused decreases in mean arterial pressure by 16±2.1% from a control of 104±2 mm Hg, and 19±2.0% from a control of 105±3 mm Hg, respectively (Fig. 1). Isosorbide dinitrate and sildenafil increased heart rate by 145±32% from a control rate of 89±10 beats/min, and 146±25% from a control rate of 87±10 beats/min, respectively (both $P<0.05$). Mean arterial pressure and heart rate returned to control level within 30 s. The prolonged decrease in mean arterial pressure in response to isosorbide dinitrate or sildenafil lasted about 15 min, without a significant change in heart

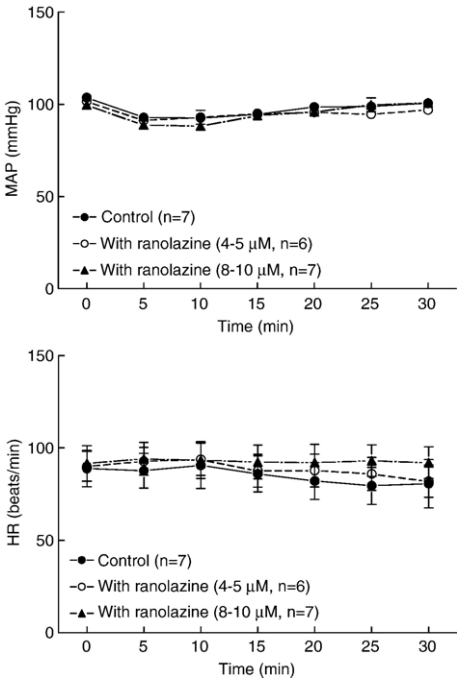


Fig. 2. Time course of changes in mean arterial pressure (top panel) and heart rate (bottom) following a bolus intravenous injection of isosorbide dinitrate (0.2 mg/kg). Isosorbide dinitrate caused a statistically significant decrease in mean arterial pressure from 5 to 15 min without a significant change in heart rate. The transient responses to isosorbide dinitrate are not included. The isosorbide dinitrate-induced hypotensive effect was not altered by either 4–5 or 8–10 μM ranolazine. Values are mean±S.E.M.

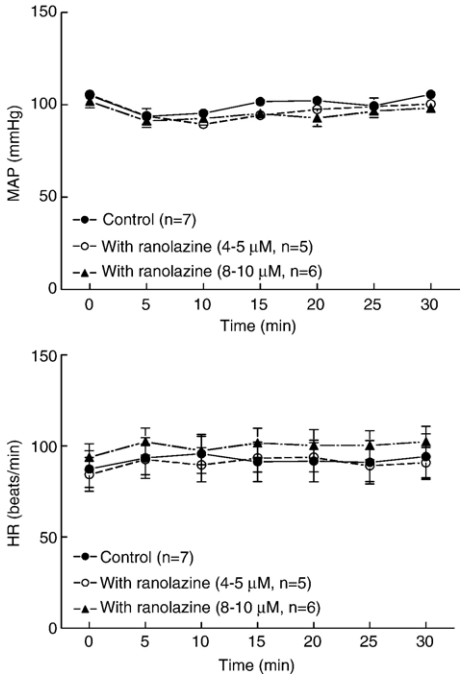


Fig. 3. Time course of changes in mean arterial pressure (top panel) and heart rate (bottom) following a bolus intravenous injection of sildenafil (0.5 mg/kg). Sildenafil caused a statistically significant decrease in mean arterial pressure from 5 to 10 min without a significant change in heart rate. The transient responses to sildenafil are not included. The sildenafil-induced hypotensive effect was not altered by either 4–5 or 8–10 μM of ranolazine. Values are mean±S.E.M.

rate. During the prolonged response, the maximum decrease in mean arterial pressure occurred between 5 (−11±0.6% for isosorbide dinitrate and −11±2.3% for sildenafil) and 10 min (−11±1.6% for isosorbide dinitrate and −9±1.8% for sildenafil) after administration of drugs.

### 3.2. Plasma concentrations and effects of ranolazine

Actual plasma concentrations of ranolazine following the intravenous administration were very close to the predicted concentrations (5 and 10 μM). An intravenous injection of ranolazine at a dose of 1.6 mg/kg, followed by an infusion of 90 μg/kg for 10 min, resulted in a mean ranolazine plasma concentration of 4.0±0.4 μM ($n$=6). There were no significant changes in mean arterial pressure and heart rate at 10 min following the administration of ranolazine (mean arterial pressure: 104±1 vs. 103±1 mm Hg; heart rate: 86±7 vs. 88±8 beats/min, $n$=6). At 30 min following the injection of isosorbide dinitrate or sildenafil, the mean ranolazine plasma concentration was 5.3±0.2 μM ($n$=6). An intravenous injection of ranolazine at a dose of 3.2 mg/kg, followed by an infusion of 170 μg/kg ranolazine for 10 min, resulted in a mean ranolazine plasma concentration of 8.3±0.5 μM ($n$=7). There were no significant changes in mean arterial pressure and heart rate at 10 min following the administration of the higher dose of ranolazine (mean arterial pressure: 102±1 vs. 101±2 mm Hg; heart rate: 87±9 vs. 90±9 beats/min, $n$=7). At 30 min after the injection of isosorbide dinitrate or sildenafil, the mean ranolazine plasma concentration was 10.4±0.7 μM ($n$=7).

### 3.3. Effects of isosorbide dinitrate or sildenafil on mean arterial pressure and heart rate during an infusion of ranolazine

The pattern and magnitude of changes in mean arterial pressure and heart rate in response to isosorbide dinitrate (0.2 mg/kg) or sildenafil (0.5 mg/kg) were similar in the absence and presence of ranolazine except for the transient tachycardia induced by sildenafil (Figs. 1–3).

In the presence of 4–5 or 8–10 μM ranolazine, the magnitudes of the transient, peak decreases in mean arterial pressure after isosorbide dinitrate injection were 21±2.8% and 19± 1.6%, respectively. Values of mean arterial pressure and heart rate in response to isosorbide dinitrate in the absence and presence of ranolazine were not significantly different. During infusions of 4–5 and 8–10 μM ranolazine, injections of isosorbide dinitrate transiently increased heart rate by 145±18 and by 140±32%, respectively. These changes were not significantly different from the changes observed after injections of isosorbide dinitrate in the absence of ranolazine. At 5 min after injections of isosorbide dinitrate during infusion of ranolazine, mean arterial pressure decreased by 10±1.6% (4–5 μM) and 11±1.0% (8–10 μM) from 102±3 and 100±2 mm Hg, respectively. At 10 min, mean arterial pressure decreased by 9±2.7% (4–5 μM) and 12±2.4% (8–10 μM) from 102±3 and 100±2 mm Hg, respectively. The time courses of changes in mean arterial pressure and heart rate following an intravenous injection of isosorbide dinitrate (0.2 mg/kg) are shown in Fig. 2.

The transient, peak increase in heart rate in response to sildenafil was significantly reduced in the presence of either 4–5 or 8–10 μM ranolazine (Δ change: 114±10 vs. 71±8 or 66±9 beats/min, both $P$<0.05, compared with sildenafil alone) as shown in Fig. 1. The transient and prolonged decreases in mean arterial pressure in response to sildenafil were not altered by either 4–5 or 8–10 μM ranolazine, as shown in Figs. 1 and 3. In the presence of ranolazine (4–5 or 8–10 μM), changes in heart rate following the injection of sildenafil were not significantly different from those in control group. The time courses of changes in mean arterial pressure and heart rate following the administration of sildenafil are shown in Fig. 3.

### 3.4. Unexpected hypotensive response to sildenafil in some conscious dogs

The intravenous bolus injection of sildenafil (0.5 mg/kg) occasionally caused a large and rapid decrease in mean arterial pressure in three of seven dogs. Although each of these three dogs received three injections of sildenafil (on different days) for a total of nine injections during three days of experiments, the large decrease in mean arterial pressure occurred only once in each dog. These responses were observed in two dogs immediately following the first administration of sildenafil (i.e., in the absence of ranolazine), and in the third dog when sildenafil was administered during a period of concurrent ranolazine infusion (at 4–5 μM). In each case, mean arterial pressure dropped below 40 mm Hg within 1.5–2.5 min after the injection of sildenafil. The decrease in mean arterial pressure was associated with a brief reflex

increase in heart rate. In all cases, the administration of epinephrine was used to raise mean arterial pressure back to control (i.e., pre-drug) levels, and the experiments were terminated. Sildenafil did not cause such a hypotensive response in the same dogs when given again on a different day. In no dog was such a hypotensive response to sildenafil observed during an infusion of the higher dose of ranolazine (8–10 μM plasma concentrations).

## 4. Discussion

The findings of this study were that isosorbide dinitrate and sildenafil caused similar changes in mean arterial pressure and heart rate following an intravenous injection: a transient decrease in mean arterial pressure and increase in heart rate, followed by a prolonged decrease in mean arterial pressure without a significant change in heart rate. Ranolazine alone had no effect on either mean arterial pressure or heart rate during intravenous infusion to achieve steady-state plasma concentrations of 4–10 μM. The pattern and magnitude of changes in mean arterial pressure and heart rate induced by either isosorbide dinitrate or sildenafil were not altered in the presence of 4–5 or 8–10 μM ranolazine, with the exception that the sildenafil-induced transient tachycardia was blunted by ranolazine.

The selection of ranolazine concentrations (5 and 10 μM) in the present study was based on our previous clinical trials, in which the largest dose of ranolazine used was 1500 mg twice daily and the recommended dose of ranolazine in the treatment of chronic angina is 1000 mg twice daily. These doses generated peak plasma ranolazine concentrations of 9.36 μM and 5.85 μM, respectively (Chaitman et al., 2004c).

The prolonged, mild hypotensive responses to isosorbide dinitrate or sildenafil that were observed in this study were consistent with results reported by previous investigators (Schwemmer et al., 2001; Yoo et al., 2002; Zoma et al., 2004). Decreases in mean arterial pressure caused by isosorbide dinitrate and sildenafil were relatively small (~10% from control). Venodilation occurring in peripheral vascular beds and a subsequent reduction of diastolic filling of the heart is a possible cause of the decrease in mean arterial pressure caused by nitrates (Wang et al., 1993), and may also be the mechanism of the prolonged hypotensive responses to isosorbide dinitrate and sildenafil that were observed in the present study.

It has been previously demonstrated that the transient increase in heart rate caused by nitrates is mediated by a baroreflex, and nitroglycerin is widely used as a tool to decrease blood pressure in studies of baroreflex function (Thames et al., 1981; Chen et al., 1992; Gori et al., 2002). However, our findings that the sildenafil-induced transient increase in heart rate was significantly blunted by either 4–5 or 8–10 μM ranolazine, whereas the sildenafil-induced transient hypotension was not affected by ranolazine, suggest that the sildenafil-induced transient increase in heart rate is not purely mediated by a baroreflex. The exact mechanism(s) responsible for the transient increase in heart rate in response to sildenafil still needs to be determined.

In three of seven dogs, sildenafil caused a rapid, large decrease in mean arterial pressure. This response was not considered attributable to ranolazine because it also occurred in two dogs when sildenafil was used alone. It has previously been observed that nitroglycerin (25 μg/kg, i.v.) caused a similar decrease in mean arterial pressure in 15–20% of conscious dogs (Hintze TH, unpublished data) when dogs were exposed to nitroglycerin for the first time. The nitroglycerin-induced hypotension could be reversed by the administration of either epinephrine or norepinephrine. In the present study, the hypotension induced by sildenafil was also reversed by epinephrine. The mechanism(s) responsible for the large, occasional hypotensive responses to sildenafil and nitroglycerin has not been determined.

In conclusion, our results indicate that ranolazine at therapeutic plasma concentrations does not alter the sustained changes in mean arterial pressure and heart rate caused by either isosorbide dinitrate or sildenafil when used in combination with either drug. These results suggest that ranolazine when used with long-acting nitrates and sildenafil does not increase their hypotensive effects.

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