Effect of the phosphodiesterase type 5 inhibitor tadalafil on pulmonary hemodynamics in a canine model of pulmonary hypertension

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ABSTRACT

Phosphodiesterase type 5 (PDE5) inhibitors are used for treating pulmonary arterial hypertension (PAH) in dogs. The long-acting PDE5 inhibitor tadalafil was recently approved for treatment of PAH in humans. Basic information related to the pharmacological and hemodynamic effects of tadalafil in dogs is scarce. In this study, the hemodynamic effects of tadalafil after intravenous (IV) and oral administration were investigated in a healthy vasoconstrictive PAH Beagle dog model induced by U46619, a thromboxane A2 mimetic. Six healthy Beagle dogs were anesthetized with propofol and maintained with isoflurane. Fluid-filled catheters were placed into the descending aorta to measure systemic arterial pressure and in the pulmonary artery to measure pulmonary arterial pressure (PAP). U46619 was infused via the cephalic vein to induce PAH.

IV infusion of U46619 significantly elevated PAP from baseline in a dose-dependent manner. U46619-elevated PAP and pulmonary vascular resistance was significantly attenuated by the simultaneous infusion of tadalafil at 100 and 200μg/kg/h. Likewise, oral administration of tadalafil at 1.0, 2.0, and 4.0 mg/kg significantly attenuated U46619-elevated PAP in a dose-dependent manner. U46619-elevated systolic and mean PAP decreased significantly 1h after oral tadalafil administration at 4.0 mg/kg, and this effect was maintained for 6h. In conclusion, tadalafil had a pharmacological effect in dogs and IV infusion of tadalafil induced pulmonary arterial relaxation, while oral administration of tadalafil decreased PAP. These results suggest that tadalafil may offer a new therapeutic option for treating dogs with PAH.

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Introduction

Pulmonary arterial hypertension (PAH) is a progressive disease characterized by chronic elevation in pulmonary arterial pressure (PAP). In veterinary medicine, PAH in dogs is defined by a systolic/mean PAP of >30/20 mmHg at rest (Johnson, 1999; Johnson et al., 1999). PAH can occur secondary to multiple abnormalities of the pulmonary or cardiovascular systems, such as left-sided heart failure, left-to-right cardiac shunting, heartworm disease, and pulmonary disease (Johnson, 1999; Glaus et al., 2004; Uchide and Saida, 2005; Bach et al., 2006; Zabka et al., 2006; Kellum and Stepfen, 2007; Seibert et al., 2010; Nakamura et al., 2011). In severe cases, PAH can lead to right-sided heart failure and death (Johnson, 1999; Johnson et al., 1999; Zabka et al., 2006).

The pathogenesis of PAH involves an imbalance between pulmonary vasoconstriction and vasodilation, which leads to increases in PAP (Humbert et al., 2004; Pietra et al., 2004). Thromboxane (TX)A2 is a potent autacoid that induces platelet aggregation and vasoconstriction, and its plasma levels are increased in animals and humans with PAH (Christman et al., 1992; Adatia et al., 1993). In dogs, an intravenous (IV) infusion of U46619, a TXA2–mimetic agent, induces pulmonary arterial constriction (Yamada et al., 1998; Gong et al., 2000; Tamura et al., 2001).

Three classes of pulmonary artery-specific vasodilators have been approved for the treatment of PAH in humans, namely, prostaglandin I2 (prostacyclin), endothelin receptor antagonists, and phosphodiesterase type 5 (PDE5) inhibitors. Of these, PDE5 inhibitors, including sildenafil, vardenafil, and tadalafil, are currently available in human medicine (Galie et al., 2009; Anderson and Nawarskas, 2010). Sildenafil has a short half-life of 4–5 h and thus requires dosing three times daily (Supuran et al., 2006; Falk et al., 2010). In veterinary medicine, sildenafil is the most frequently used PDE5 inhibitor for treatment of PAH. It reportedly improves
symptoms and clinical outcomes in dogs with PAH (Bach et al., 2006; Kellum and Stepien, 2007; Brown et al., 2010; Nakamura et al., 2011).

In contrast, tadalafil has a longer half-life of 17.5 h that allows for once-daily dosing (Supuran et al., 2006; Arif and Poon, 2011); it is currently approved for the treatment of PAH and erectile dysfunction in humans (Porst et al., 2003; Skoumal et al., 2004). Tadalafil may present a new therapeutic option for PAH in dogs because of its less frequent dosing and more sustained benefits. However, only one case report has described the use of tadalafil for the treatment of PAH in dogs (Serras et al., 2006). Basic information on the pharmacological and hemodynamic effects of tadalafil as a treatment for PAH in dogs remains scarce. In the present study, to clarify its pulmonary hemodynamic action, we investigated the effects of tadalafil on PAH and vascular resistance in healthy dogs with U46619-induced acute vasoconstrictive PAH.

Materials and methods

Animals

This study was approved by the Institutional Animal Care and Use Committee for Kitasato University (approval number 13-123, 5 December 2013). Six Beagle dogs were used in this study (3 males, 3 females; aged 4–5 years; weight 10–13 kg). All dogs were determined to be healthy according to the results of complete physical and echocardiography examinations. The dogs were housed individually in cages and fed commercial dry food with free access to water.

Drugs

U46619 (S,11-dideoxy-11a,9a-epoxymethanoprostaglandin F2α; U46619, Cayman) was dissolved in ethanol according to the manufacturer’s instructions. Tadalafil (Tadalafil, Acanthus Research) was dissolved in dimethyl sulfoxide (DMSO) for IV infusion or purchased for oral administration (Adcirca 20 mg). Immediately before examination, each drug was diluted in sterile saline to a final concentration of 50 μg/mL (for U46619) and 0.2 mg/mL (for tadalafil), respectively.

Anesthesia

The dogs were sedated with butorphanol (0.2 mg/kg IV), diazepam (0.5 mg/kg SC) and atropine (0.025 mg/kg SC); anesthetized with propofol (6.0 mg/kg IV); and intubated. Anesthesia was maintained using a mixture of 2.0–3.0% isoflurane and oxygen. The end-tidal partial pressure of carbon dioxide in arterial blood (Paco2) and hemoglobin saturation level of oxygen (SPO2) were monitored and maintained between 35–45 mmHg and 95–100%, respectively. Heart rate was monitored using electrocardiography (COLIN BP-608, Nihon Kohden). Respiratory rate was maintained between 10 and 20 breaths/min. Fluid loss was replaced by IV infusion of Ringer’s solution, and the total fluid volume was adjusted to 60 mL/kg/day. Following the examinations, the dogs were allowed to recover from anesthesia.

Hemodynamic measurements

The anesthetized dogs were positioned in left lateral recumbency. A 3-Fr fluid-filled catheter was placed via the left femoral artery into the descending aorta to measure systolic, mean, and diastolic systemic arterial pressure (SAP). A 4-Fr fluid-filled catheter or a Swan–Ganz catheter (5 Fr thermodilution catheter, TC-504, Nihon Kohden) was inserted through the jugular vein and advanced into the pulmonary artery to measure the systolic, mean, and diastolic PAP. Similarly, mean right ventricular pressure (RVP) and mean central venous pressure (CVP) were also measured.

Mean pulmonary capillary wedge pressure (PCWP) and cardiac output (CO) were measured using a Swan–Ganz catheter. CO was calculated as the average of the three measurements obtained by thermodilution (CCOM monitor, CO-203, Terumo) with an injection of 5 mL of normal saline kept at 4 °C (Gong et al., 2000; Tamura et al., 2007).

Pulmonary vascular resistance (PVR), systemic vascular resistance (SVR), and PVR to SVR ratio (Rpv/Rsv ratio) were calculated using the following formulae (Tamura et al., 2001):

\[
PVR = \frac{\text{mean PAP} - \text{mean PCWP}}{\text{CO}}
\]

\[
SVR = \frac{\text{mean SAP} - \text{mean CVP}}{\text{CO}}
\]

\[
\text{Rpv/Rsv ratio} = \frac{\text{PVR}}{\text{SVR}}
\]

All pressures were measured using fluid-filled transducers (TruWave Disposable Pressure Transducer, Nihon Kohden) and recorded by polygraphy (Omniace RT 3200, NEC). After completing the procedures, a 20- to 30-min equilibration period was allowed to stabilize hemodynamics. Heart rate, SPO2 and blood pressures were recorded initially as a baseline.

Study protocols

Study 1

The infusion rates of U46619 were established based on previous reports (Yamada et al., 1998; Tamura et al., 2001). U46619 was infused at rates of 0.1, 0.3, 0.6 and 0.9 μg/kg/min for 10–20 min via the cephalic vein. SAP and PAP were measured under anesthesia.

Study 2

After pretreatment with IV U46619 (0.9 μg/kg/min) for 10 min, tadalafil was infused simultaneously at rates of 50, 100, and 200 μg/kg/min for 10 min. The infusion rate of U46619 was maintained until the end of tadalafil infusion. This study was conducted with a crossover design. The order of tadalafil administration (50, 100, and 200 μg/kg/1h) was randomly assigned to each dog. After completing the first procedure, a stabilization period of at least 30 min was provided to re-establish a stable baseline condition. The dogs were then randomly assigned to receive one of the remaining treatments, and each dog received each of the three doses. SAP was measured using a fluid-filled catheter and PAP, mean RVP, mean CVP, mean PCWP and CO were measured with a Swan–Ganz catheter under anesthesia. SVR, PVR, and the Rp/Rs ratio were calculated.

Study 3

The dose-dependent effects of oral tadalafil were determined. The dogs were divided into three groups, namely, placebo, U46619 and tadalafil. A single dose of placebo (for the placebo and U46619 groups) was administered orally. Tadalafil was administered orally at 1.0, 2.0, and 4.0 mg/kg in the tadalafil group. PAP was measured under anesthesia 3 h after administration.

Study 4

The time-dependent effects of oral tadalafil were determined 1, 2, 3, and 6 h after oral administration. The dogs were divided into three groups, namely, placebo, U46619 and tadalafil. A single dose of placebo (for the placebo and U46619 groups) was administered orally. Similarly, tadalafil at 4.0 mg/kg was administered orally to the tadalafil group. PAP was measured under anesthesia.

In Studies 3 and 4, U46619 (0.9 μg/kg/min) was simultaneously infused for 10 min at each time point in the U46619 and tadalafil groups. Sterile saline was administered for 10 min in the control group. Both studies were conducted with a crossover design. Each drug was given randomly, and the interval between treatments was at least 3 days. After each washout period, the dogs were then randomly assigned to receive one of the remaining treatments. This continued until each dog had received all treatments.

Statistical analyses

Normality of data was assessed with the Kolmogorov–Smirnov test. Data are presented as means ± standard deviation (SD). One-way analysis of variance (ANOVA) was used to compare the results among the groups in Studies 1, 2, and 3. In Study 4, one-factor repeated measures ANOVA was used to compare the time-dependent changes in heart rate and PAP with the baseline values. Two-way ANOVA was used to compare the time-dependent changes in PAP among the groups. The significance of the differences between the mean values of the each condition was tested with Tukey’s multiple-comparison test. P < 0.05 was considered statistically significant.

Results

As baseline values before the induction of anesthesia, mean heart rate was 115 ± 29 beats/min, respiratory rate 41 ± 33 breaths/min and body temperature 38.7 ± 0.2 °C.

The dose-dependent hemodynamic effects of IV U46619 in Study 1 are shown in Fig. 1. SPO2 remained unchanged during the study (baseline; 97.5 ± 1.5%, 0.1 μg/kg/min; 97.5 ± 1.3%, 0.3 μg/kg/min; 98.2 ± 0.8%, 0.6 μg/kg/min; 98.3 ± 0.8%, 0.9 μg/kg/min; 98.3 ± 1.4%). Compared with baseline, the heart rate and SAP did not change with IV infusion of U46619. In contrast, IV infusion of U46619 changed the PAP in a dose-dependent manner from baseline. Systolic PAP was significantly higher than baseline at U46619 infusion rates of 0.6 and 0.9 μg/kg/min. The mean and diastolic PAP were also significantly higher than baseline at infusion rates of 0.3, 0.6 and 0.9 μg/kg/min.

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The hemodynamic effects of simultaneous infusion of tadalafil and U46619 were investigated in Study 2. U46619-elevated systolic, mean and diastolic PAP were slightly lower with simultaneous infusion of tadalafil at 50μg/kg/h. In contrast, U46619-elevated systolic, mean and diastolic PAP were significantly lower with simultaneous infusion of tadalafil at 100 and 200μg/kg/h (Fig. 2). Changes in the other hemodynamic measurements are shown in Table 1. The heart rate did not change with U46619 and/or any dose of tadalafil. The SAP increased with U46619, but the change was not statistically significant. SAP did not change with simultaneous infusion of any dose of tadalafil. U46619 significantly increased the RVP, CVP and PCWP from baseline, but these parameters were not changed by simultaneous infusion of tadalafil. The CO decreased with U46619, but the change was not statistically significant; CO did not change with simultaneous infusion of any dose of tadalafil. As a result, although U46619 significantly increased PVR and SVR from baseline, simultaneous infusion of tadalafil at 50, 100 and 200μg/kg/h resulted in a significantly lower PVR than that seen with U46619 and/or any dose of tadalafil.

Table 1

| Hemodynamic effects of intravenous infusion of tadalafil and U46619. |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Baseline | U46619 | U46619 + tadalafil |
| Heart rate (bpm) | 116 ± 21 | 104 ± 18 | 102 ± 18 | 102 ± 19 | 99 ± 19 |
| SPO2 (%) | 97.5 ± 1.5 | 97.5 ± 1.5 | 98.2 ± 0.8 | 98.3 ± 0.8 | 98.3 ± 1.4 |
| Systolic SAP (mmHg) | 96 ± 22 | 108 ± 22 | 105 ± 13 | 105 ± 13 | 111 ± 17 |
| Mean SAP (mmHg) | 68 ± 13 | 82 ± 13 | 82 ± 12 | 82 ± 5 | 88 ± 13 |
| Diastolic SAP (mmHg) | 53 ± 10 | 74 ± 9 | 73 ± 11 | 73 ± 4 | 83 ± 5 |
| Mean RVP (mmHg) | 3.4 ± 3.5 | 12.4 ± 3.4<sup>a</sup> | 8.9 ± 2.8<sup>a</sup> | 8.7 ± 2.8<sup>a</sup> | 8.4 ± 3.1<sup>a</sup> |
| Mean CVP (mmHg) | −0.1 ± 1.7 | 3.7 ± 2.1<sup>a</sup> | 3.3 ± 2.1<sup>a</sup> | 3.7 ± 2.2<sup>b</sup> | 3.3 ± 2.2<sup>a</sup> |
| Mean PCWP (mmHg) | 1.8 ± 2.9 | 8.7 ± 4.3<sup>a</sup> | 8.3 ± 4.0<sup>a</sup> | 6.3 ± 3.5 | 6.3 ± 3.4 |
| CO (L/min) | 1.7 ± 0.6 | 11 ± 0.4 | 1.2 ± 0.5 | 1.1 ± 0.4 | 1.2 ± 0.4 |
| SVR (dyn/s/cm<sup>5</sup>) | 49.4 ± 16.3 | 71.8 ± 30.6<sup>a</sup> | 84.4 ± 39.0<sup>a</sup> | 87.0 ± 28.2<sup>a</sup> | 88.1 ± 29.1<sup>a</sup> |

Data are shown as means ± standard deviation (SD). Baseline represents data before drug administration under anesthesia in each group. SAP, systemic arterial pressure; RVP, right ventricular pressure; CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure; CO, cardiac output; SVR, systemic vascular pressure.

<sup>a</sup> P < 0.05 vs. baseline.
<sup>b</sup> P < 0.01 vs. baseline.
<sup>c</sup> P < 0.001 vs. baseline.
U46619 (Fig. 3). Similarly, the Rp/Rs ratio was significantly higher than baseline with U46619 and significantly lower with simultaneous infusion of tadalafil than that seen with U46619 (Fig. 3).

The dose-dependent effects on PAP 3 h after a single oral administration of tadalafil were investigated in Study 3 (Fig. 4, Table 2). Oral administration of tadalafil alone did not change the systolic, mean or diastolic PAP or heart rate compared with placebo. U46619-elevated systolic, mean, and diastolic PAP did not change by oral administration of tadalafil at 1.0 mg/kg. In contrast, the U46619-elevated systolic, mean, and diastolic PAP were significantly lower with prior oral administration of tadalafil at 2.0 and 4.0 mg/kg.

Based on the results of study 3, the time-dependent effects on PAP after a single oral administration of tadalafil were investigated in Study 4 (Fig. 5, Table 3). Neither U46619 infusion nor oral tadalafil changed the heart rate from baseline. U46619 significantly elevated the systolic, mean and diastolic PAP for 6 h compared to baseline. Despite prior administration of tadalafil at 4.0 mg/kg, the U46619 infusion significantly elevated the systolic, mean and diastolic PAP from 1 to 6 h. However, oral tadalafil administration significantly decreased U46619-elevated systolic and diastolic PAP at 3 and 6 h compared to the U46619 group. Similarly, oral tadalafil significantly decreased U46619-elevated mean PAP at 1 h and until 6 h.

Discussion

The pathogenesis of PAH is poorly understood, but an imbalance between vasoconstriction and vasodilation contributes to the development of PVR (Humbert et al., 2004; Pietra et al., 2004; Kellihan and Stepien, 2012). For example, TXA2 is a potent autacoid that induces platelet aggregation and vasoconstriction, and there is experimental and clinical evidence that its plasma levels are increased in animals and humans with PAH (Christman et al., 1992; Adatia et al., 1993).

U46619, a TXA2-mimetic agent, increased PVR in isolated canine lungs (Stephenson et al., 1998), indicating that U46619 directly stimulates vasoconstriction of the pulmonary artery. In the present study, an IV infusion of U46619 significantly elevated PAP in a dose-dependent manner. In addition, U46619 at a rate of 0.9 μg/kg/min significantly elevated PVR and particularly the Rp/Rs ratio from baseline suggesting that U46619 stimulates pulmonary arterial constriction in dogs and that the pulmonary artery is a main target of TXA2 (Yamada et al., 1998; Gong et al., 2000; Tamura et al., 2001).

In addition to its effect on the pulmonary artery, U46619 significantly elevated SAP, significantly elevated PCWP and SVR and insignificantly decreased CO. Similar to our results, a previous study...

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**Table 2**

Dose-dependent effects on heart rate and pulmonary arterial pressure (PAP) after oral administration of tadalafil.

<table>
<thead>
<tr>
<th>Control</th>
<th>U46619</th>
<th>Tadalafil</th>
<th>U46619 + tadalafil</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.9 μg/kg</td>
<td>1 mg/kg</td>
<td>2 mg/kg</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>116 ± 21</td>
<td>111 ± 23</td>
<td>111 ± 23</td>
</tr>
<tr>
<td>Systolic PAP (mmHg)</td>
<td>70 ± 3.9</td>
<td>29.6 ± 6.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>8.7 ± 3.4</td>
</tr>
<tr>
<td>Mean PAP (mmHg)</td>
<td>4.4 ± 2.8</td>
<td>21.4 ± 2.5&lt;sup&gt;e&lt;/sup&gt;</td>
<td>3.3 ± 1.7</td>
</tr>
<tr>
<td>Diastolic PAP (mmHg)</td>
<td>18 ± 2.3</td>
<td>15.2 ± 2.8&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0.7 ± 1.4</td>
</tr>
</tbody>
</table>

Data are shown as means ± standard deviation (SD). bpm, beats/min.

<sup>a</sup> P < 0.01 vs. control.
<sup>b</sup> P < 0.001 vs. baseline.
<sup>c</sup> P < 0.05 vs. U46619.
<sup>d</sup> P < 0.001 vs. U46619.

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**Fig. 3.** Changes in pulmonary vascular resistance (PVR) with simultaneous infusion of tadalafil and U46619. Data are shown as means ± standard deviation (SD). BL, baseline; U46, U46619; Rp/Rs ratio, pulmonary resistance to systemic arterial resistance ratio. <sup>a</sup> P < 0.01 vs. baseline, <sup>b</sup> P < 0.001 vs. baseline, <sup>c</sup> P < 0.05 vs. U46619, <sup>d</sup> P < 0.01 vs. U46619.

**Fig. 4.** Dose-dependent changes in systolic pulmonary arterial pressure (PAP) after oral administration of tadalafil. Data are shown as means ± standard deviation (SD). U46619 was infused at a rate of 0.9 μg/kg/min for 10 min at 3 h after oral administration of each drug: U46, U46619; PL, placebo. <sup>a</sup> P < 0.001 vs. control, <sup>b</sup> P < 0.05 vs. U46619, <sup>c</sup> P < 0.001 vs. U46619.

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demonstrated that the SAPs, SVR and PCWP increased following infusion of U46619 as CO decreases (Gong et al., 2000). U46619 produced concentration-dependent contractions in canine isolated coronary, mesenteric and femoral arteries, which were inhibited by a TXA₂ antagonist (Matsuzaki et al., 1992). These results indicate that U46619 stimulates systemic arterial constriction in addition to its effect on the pulmonary artery. U46619-elevated systemic arterial constriction and decreased CO might lead to an increase in PCWP.

Tadalafil, a specific PDE5 inhibitor, has greater affinity for PDE5 compared to other PDE5 inhibitors (Corbin and Francis, 2002; Francis and Corbin, 2003) and induces a significant reduction in PAP and PVR in patients with PAH (Ghofrani et al., 2004; Mukhopadhyay et al., 2006). PDE5 is located primarily in the corpora cavernosa of the penis and pulmonary arterial smooth muscle (Senzaki et al., 2001). Its main role is to degrade cyclic guanosine monophosphate (cGMP) in these tissues. PDE5 inhibition increases cGMP bioavailability, which causes smooth muscle relaxation and decreased vasmotor tone (Francis and Corbin, 1999; Lincoln et al., 2001). In the present study, IV infusion of tadalafil significantly decreased the U46619-elevated PAP and PVR in dogs with PAH (Ghofrani et al., 2004; Forgue et al., 2006; Mukhopadhyay et al., 2006). In contrast, pharmacokinetic data for tadalafil in dogs remains scarce. The current study demonstrated that oral tadalafil at a dosage of 4 mg/kg showed a maximum effect. Thus, we deliberately chose a high dose to induce a marked hemodynamic effect and determine the time-dependent effects of tadalafil. Oral tadalafil significantly decreased U46619-elevated mean PAP at 1 h, and this effect was maintained for 6 h. These results indicate that oral administration of tadalafil in dogs was efficacious within 1 h and that the effect is maintained for at least 6 h. However, further studies are required to clarify the pharmacokinetics of tadalafil in dogs.

Our study has several limitations. We could not exclude the possibility that general anesthesia may have modulated the hemodynamic effects of tadalafil. Although oral tadalafil at 2 and 4 mg/kg lowered the U46619-induced increase in PAP, the optimum clinical dosage remains unknown. Reportedly, common side effects in humans, including headache, facial flushing, nasal congestion, dyspepsia, and transient visual impairment, have been associated with tadalafil administration (Supuran et al., 2006). The current study did not evaluate the potential chronic effects and side effects of tadalafil in dogs.

**Table 3**

<table>
<thead>
<tr>
<th>Time-dependent effects on heart rate and pulmonary arterial pressure (PAP) after oral administration of tadalafil.</th>
<th>Heart rate (bpm)</th>
<th>Baseline</th>
<th>1 h</th>
<th>3 h</th>
<th>6 h</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control</strong></td>
<td>118 ± 27</td>
<td>116 ± 28</td>
<td>103 ± 34</td>
<td>106 ± 29</td>
<td></td>
</tr>
<tr>
<td><strong>U46619</strong></td>
<td>117 ± 25</td>
<td>112 ± 18</td>
<td>110 ± 20</td>
<td>100 ± 25</td>
<td></td>
</tr>
<tr>
<td><strong>U46619 + tadalafil</strong></td>
<td>116 ± 20</td>
<td>119 ± 13</td>
<td>108 ± 19</td>
<td>117 ± 24</td>
<td></td>
</tr>
<tr>
<td><strong>Mean PAP (mmHg)</strong></td>
<td>Baseline</td>
<td>1 h</td>
<td>3 h</td>
<td>6 h</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>3.9 ± 2.3</td>
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<td>U46619 + tadalafil</td>
<td>3.2 ± 2.1</td>
<td>14.5 ± 3.1</td>
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<td>15.4 ± 3.5</td>
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<tr>
<td><strong>Diastolic PAP (mmHg)</strong></td>
<td>Baseline</td>
<td>1 h</td>
<td>3 h</td>
<td>6 h</td>
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<tr>
<td>Control</td>
<td>0.9 ± 1.2</td>
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<td>U46619</td>
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<tr>
<td>U46619 + tadalafil</td>
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<td>10.4 ± 3.3</td>
<td>8.8 ± 3.2</td>
<td>10.7 ± 2.9</td>
<td></td>
</tr>
</tbody>
</table>

Data are shown as means ± standard deviation (SD). Baseline represents data before drug administration under anesthesia in each group. bpm, beats/min.

a) *P < 0.001 vs. baseline at the same time point.

b) *P < 0.05 vs. U46619 at the same time point.

**Fig. 5.** Time-dependent changes in systolic pulmonary arterial pressure (PAP) after oral administration of tadalafil. Data are shown as means ± standard deviation (SD). BL, baseline. Baseline represents data before drug administration under anesthesia in each group. a) *P < 0.001 vs. baseline, b) *P < 0.01 vs. baseline, c) *P < 0.001 vs. baseline at the same time point.

**Fig. 6.** Time-dependent changes in mean pulmonary arterial pressure (PAP) after oral administration of tadalafil. Data are shown as means ± standard deviation (SD). BL, baseline. Baseline represents data before drug administration under anesthesia in each group. a) *P < 0.001 vs. baseline, b) *P < 0.01 vs. baseline, c) *P < 0.001 vs. baseline at the same time point.

**Table 4**

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<tr>
<td><strong>Mean PAP (mmHg)</strong></td>
<td>Baseline</td>
<td>1 h</td>
<td>3 h</td>
<td>6 h</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>3.9 ± 2.3</td>
<td>3.7 ± 2.7</td>
<td>5.1 ± 2.3</td>
<td>4.1 ± 1.6</td>
<td></td>
</tr>
<tr>
<td>U46619</td>
<td>4.4 ± 2.6</td>
<td>19.3 ± 3.0</td>
<td>20.7 ± 3.1</td>
<td>20.2 ± 2.1</td>
<td></td>
</tr>
<tr>
<td>U46619 + tadalafil</td>
<td>3.2 ± 2.1</td>
<td>14.5 ± 3.1</td>
<td>14.8 ± 3.0</td>
<td>15.4 ± 3.5</td>
<td></td>
</tr>
<tr>
<td><strong>Diastolic PAP (mmHg)</strong></td>
<td>Baseline</td>
<td>1 h</td>
<td>3 h</td>
<td>6 h</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0.9 ± 1.2</td>
<td>0.9 ± 1.4</td>
<td>1.3 ± 2.0</td>
<td>0.6 ± 0.9</td>
<td></td>
</tr>
<tr>
<td>U46619</td>
<td>1.3 ± 2.0</td>
<td>13.9 ± 3.2</td>
<td>13.8 ± 4.1</td>
<td>14.7 ± 2.7</td>
<td></td>
</tr>
<tr>
<td>U46619 + tadalafil</td>
<td>0.4 ± 1.0</td>
<td>10.4 ± 3.3</td>
<td>8.8 ± 3.2</td>
<td>10.7 ± 2.9</td>
<td></td>
</tr>
</tbody>
</table>

Data are shown as means ± standard deviation (SD). Baseline represents data before drug administration under anesthesia in each group. bpm, beats/min.

a) *P < 0.001 vs. baseline at the same time point.

b) *P < 0.05 vs. U46619 at the same time point.

**Conclusions**

IV infusion of tadalafil decreased U46619-elevated PAP and PVR in dogs without changes in SAP and SVR. Oral administration of tadalafil alone did not change PAP, but decreased U46619-elevated PAP 1 h after oral administration and the effect was maintained for 6 h. The results suggest that tadalafil improved U46619-induced pulmonary arterial constriction, leading to pulmonary arterial relaxation.

**Conflict of interest statement**

None of the authors of this paper has a financial or personal relationship with other people or organizations that could inappropriately influence or bias the content of the paper.
References


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