Sodium tanshinone IIA sulfonate increased intestinal hemodynamics without systemic circulatory changes in healthy newborn piglets

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Liu JQ, Morton J, Miedzyblocki M, Lee TF, Bigam DL, Fok TF, Chen C, Lee SK, Davidge ST, Cheung PY. Sodium tanshinone IIA sulfonate increased intestinal hemodynamics without systemic circulatory changes in healthy newborn piglets. Am J Physiol Heart Circ Physiol 297:H1217–H1224, 2009. First published July 17, 2009; doi:10.1152/ajpheart.00477.2009.—In traditional Chinese medicine, tanshinone IIA is a lipid-soluble component of Danshen that has been widely used for various cardiovascular and cerebrovascular disorders, including neonatal asphyxia. Despite promising effects, little is known regarding the hemodynamic effects of tanshinone IIA in newborn subjects. To examine the dose-response effects of sodium tanshinone IIA sulfonate (STS) on systemic and regional hemodynamics and oxygen transport, 12 newborn piglets were anesthetized and acutely instrumented for the placement of femoral arterial and venous, pulmonary arterial catheters to measure mean arterial, central venous, pulmonary arterial pressures, respectively. The blood flow at the common carotid, renal, pulmonary, and superior mesenteric (SMA) arteries were continuously monitored after treating the piglets with either STS (0.1–30 mg/kg iv) or saline treatment (n = 6/group). To further delineate the underlying mechanisms for vasorelaxant effects of STS, in vitro vascular myography was carried out to compare its effect on rat mesenteric and carotid arteries (n = 4–5/group). STS dose-dependently increased the SMA blood flow and the corresponding oxygen delivery with no significant effect on systemic and pulmonary, carotid and renal hemodynamic parameters. In vitro studies also demonstrated that STS selectively dilated rat mesenteric but not carotid arteries. Vasodilation in mesenteric arteries was inhibited by apamin and TRAM-34 (calcium-activated potassium channel inhibitors) but not by meclofenamate (cyclooxygenase inhibitor) or N-nitro-L-arginine methyl ester hydrochloride (nitric oxide synthase inhibitor). In summary, without significant hemodynamic effects on newborn piglets, intravenous infusion of STS selectively increased mesenteric perfusion in a dose-dependent manner, possibly via an endothelium-derived hyperpolarizing factor vasodilating pathway.

N-nitro-L-arginine methyl ester hydrochloride; common carotid artery

DANSHEN IS THE DRIED ROOT of Salvia miltiorrhiza (Fam. Labiatae) and is commonly used in traditional Chinese medicine for the treatment of various cardiovascular and cerebrovascular diseases, including myocardial infarct, angina pectoris, coronary heart disease, and cerebral stroke (6, 11, 35). Among the ingredients, tanshinone IIA is the most abundant and well-studied lipophilic compound of Danshen (3). In regard to its cardiovascular effects, tanshinone IIA has been shown to cause coronary vasodilatation, reduce myocardial infarct size (21, 28), cardiomyocyte apoptosis (9), and hypertrophy (32), as well as to inhibit platelet aggregation (13). In critically ill neonates such as those with asphyxia, there is increasing evidence that ischemia-reperfusion injury contributes to some clinico-pathological complications, including shock, hypoxic-ischemic encephalopathy (HIE), and necrotizing enterocolitis (NEC) (23, 26, 27). Indeed, the pathogenesis of HIE and NEC has been suggested to be related to regional ischemia, and improving cerebral and mesenteric perfusion during recovery may be an effective therapeutic approach in the management of asphyxiated neonates (4, 23). Thus tanshinone IIA may have a therapeutic potential for asphyxiated neonates, including the possible improvement of systemic and regional perfusion. However, there is a lack of knowledge regarding the hemodynamic effects of tanshinone IIA and/or its derivatives in newborn subjects.

To address the potential for clinical use, it is essential to understand the dose-response of tanshinone IIA in newborn subjects. In view of the vascular effect of tanshinones, we aimed to investigate the dose-response of tanshinone IIA in systemic, pulmonary, and regional circulations in acutely instrumented newborn piglets. This information may help to determine if tanshinone IIA is a potential therapy that can specifically target one vascular bed without systemic effects. Furthermore, we used in vitro myography to investigate vascular bed specificity and to determine potential mechanisms of tanshinone IIA-induced vasodilation.

MATERIALS AND METHODS

All experiments were conducted in accordance with the guidelines of Canadian Council of Animal Care (2000) and were approved by the Animal Care and Use Committee, University of Alberta.

Materials. Twelve mixed-breed piglets (1–4 days of age, weighing 1.6–2.3 kg) were used for in vivo hemodynamic study. Spague-Dawley rats (3–4 mo of age, weighing 400–600 g) were used for in vitro vascular myography. Sodium tanshinone IIA sulfonate (STS, molecular formula C19H17NaO6S, mol wt 396.39, purity 98%), a water-soluble derivative of Danshen, was purchased from Topharman Shanghai. The STS solution was freshly prepared daily with sterilized water before use. The pH of STS solution was 3.8 ± 0.1.

Animal preparation. Spontaneously breathing piglets were anesthetized initially via inhaled isoflurane (2–3%). Inhalational anesthe-
Table 1. Effect of STS on arterial blood gas

<table>
<thead>
<tr>
<th>Time (min):</th>
<th>STS, mg/kg</th>
<th>Control</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>5</th>
<th>6</th>
<th>10</th>
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<th>20</th>
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<tbody>
<tr>
<td>Baseline</td>
<td>7.38 ± 0.02</td>
<td>7.41 ± 0.01</td>
<td>7.42 ± 0.01</td>
<td>7.42 ± 0.02</td>
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<tr>
<td>STS</td>
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<td>39 ± 1</td>
<td>36 ± 1</td>
<td>36 ± 1</td>
<td>37 ± 2</td>
<td>38 ± 1</td>
<td>38 ± 1</td>
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<tr>
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<td>64 ± 3</td>
<td>66 ± 2</td>
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<tr>
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<td>16 ± 2</td>
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</table>

Values are means ± SE. STS, sodium tanshinone IIA sulfonate. All P > 0.05, STS vs. control (2-way ANOVA).

Table 2. Effects of STS on systemic and pulmonary haemodynamics

<table>
<thead>
<tr>
<th>Time (min):</th>
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<th>1</th>
<th>2</th>
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<td>190 ± 12</td>
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<tr>
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<td>91 ± 0.08</td>
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<td>0.90 ± 0.09</td>
<td>0.90 ± 0.09</td>
<td>0.93 ± 0.09</td>
<td>0.93 ± 0.09</td>
<td>0.98 ± 0.07</td>
<td>1.00 ± 0.09</td>
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<td>0.44 ± 0.04</td>
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<td>0.34 ± 0.02</td>
<td>0.31 ± 0.02</td>
<td>0.30 ± 0.02</td>
<td>0.29 ± 0.02</td>
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</tr>
<tr>
<td>Control</td>
<td>0.37 ± 0.04</td>
<td>0.16 ± 0.03</td>
<td>0.17 ± 0.04</td>
<td>0.17 ± 0.04</td>
<td>0.17 ± 0.04</td>
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</tr>
</tbody>
</table>

Values are means ± SE. *P < 0.05 vs. baseline (1-way ANOVA). All P > 0.05, STS vs. control (2-way ANOVA).
orative heat loss. Heart rate, cardiac output, MAP, PAP, CVP and common carotid artery (CCA), pulmonary arterial, SMA and renal artery (RA) flows were continuously monitored, and all data were recorded by a DT 2801-A analog-to-digital converter board (Data Translation, Ontario, Canada). For each hemodynamic parameter, an average of a 2-min range at the end of administration of each dosage during the experimental period was taken.

**Experimental protocol.** After 60 min of stabilization, piglets were randomized into either a control or a STS-treated group (n = 6/group). Based on dosages reported in the literature (1–10 mg/kg iv and 2–60 mg/kg ip in rats) (2), an intravenous dosage range of 0.1–30 mg/kg was selected in the present study. The doses of STS were given in an accumulated dose manner (0.1, 0.3, 1, 3, 10, or 30 mg/kg) stepping up every 30 min for a total duration of 3 h. Because the plasma concentration of STS peaked within 30 min after intravenous injection in rats (2), the physiological changes after any given dose were observed for 30 min. The total injection volume of STS was 10 ml; 5 ml (50% of the dose) were given over 5 min as a bolus, whereas another 5 ml (the remaining 50% dose) were infused over 25 min. The control group received the same volume of 0.9% normal saline (pH 5.5). At the end of the study, piglets were killed with an overdose of pentobarbital sodium (100 mg/kg iv).

**Hemodynamic measurements and oxygen transport.** The pulmonary arterial, CCA, SMA and RA blood flows were indexed with piglet weight and expressed as cardiac index (CI), common carotid artery flow index, superior mesenteric artery flow index, and renal artery flow index (units: ml·kg\(^{-1}\)·min\(^{-1}\)), respectively. The hemodynamic variables were calculated as follows:

\[
\text{Systemic oxygen delivery (ml O}_2\cdot\text{kg}^{-1}\cdot\text{min}^{-1}) = \text{CI} \times \text{SaO}_2 \times 1.34 \times [\text{Hb}],
\]

\[
\text{Systemic oxygen consumption (ml O}_2\cdot\text{kg}^{-1}\cdot\text{min}^{-1}) = \text{CI} \times (\text{SaO}_2 - \text{SvO}_2) \times 1.34 \times [\text{Hb}],
\]

\[
\text{Systemic oxygen extraction ratio} (%) = \frac{[\text{SaO}_2 - \text{SvO}_2]}{\text{SaO}_2} \times 100%.
\]

Simultaneous blood samples were drawn for evaluation of blood gases, arterial and mixed venous oxygen saturation by ABL500 and OSM 3 Hemoximeter (Radiometer, Copenhagen, Denmark) at the same time points. Based on the blood gas saturation [arterial saturation (SaO\(_2\)); venous saturation (SvO\(_2\))] and hemoglobin (Hb) concentration, the oxygen delivery and consumption were calculated as follows.

Carotid arterial oxygen delivery (ml O\(_2\)·kg\(^{-1}\)·min\(^{-1}\))

\[
= \text{CCA flow index} \times \text{SaO}_2 \times 1.34 \times [\text{Hb}],
\]

where \([\text{Hb}]\) is Hb concentration.

Superior mesenteric arterial oxygen delivery (ml O\(_2\)·kg\(^{-1}\)·min\(^{-1}\))

\[
= \text{SMA flow index} \times \text{SaO}_2 \times 1.34 \times [\text{Hb}],
\]

Renal arterial oxygen delivery (ml O\(_2\)·kg\(^{-1}\)·min\(^{-1}\))

\[
= \text{RA flow index} \times \text{SaO}_2 \times 1.34 \times [\text{Hb}],
\]

Stroke volume index (ml·kg\(^{-1}\)·beat\(^{-1}\)) = CI/heart rate.

**Fig. 1.** Cumulative dose effect of sodium tanshinone IIA sulfonate [STS (●), n = 6] on mean arterial pressure (MAP; A), mean pulmonary arterial pressure (PAP; B), and the PAP-to-MAP ratio (C) compared with saline [control (○)] (P > 0.05, 2-way ANOVA). #P < 0.05 vs. baseline (1-way ANOVA).
Systemic vascular resistance index
\[ \text{mmHg} \cdot \text{ml}^{-1} \cdot \text{min}^{-1} \cdot \text{kg}^{-1} = (\text{MAP} - \text{CVP})/\text{CI} \] (8)

Pulmonary vascular resistance index
\[ \text{mmHg} \cdot \text{ml}^{-1} \cdot \text{min}^{-1} \cdot \text{kg}^{-1} \] was estimated by PAP/CI (9)

*In vitro vascular myography.* Small mesenteric (129 ± 6 μm) and carotid (675 ± 23 μm) arteries were isolated from young male Sprague-Dawley rats. The arteries were mounted on two 25-μm wires attached to a wire myograph (DMT; Copenhagen, SV, Denmark) to allow isometric tension recordings. Vessels were normalized to determine their optimal resting tension.

Following a 30-min equilibration period, vessels were exposed two times to a single concentration of phenylephrine (10 μM) followed by a single concentration of methylcholine (3 μM) to check functional endothelial and smooth muscle integrity. A concentration-response curve (CCRC) to either phenylephrine (mesenteric arteries) or U-46619 (carotid arteries) was performed to determine the EC80 for each vasoconstrictor. Vasocostrictors were chosen based on our previous studies demonstrating arterial bed specific responses to adrenergic agonists. Pilot data using STS showed vasodilation was not dependent on the vasoconstrictor agonist used. To investigate vascular responses to STS (1–300 μM), a CCRC was performed following preconstriction with either phenylephrine or U-46619. To determine if vasodilator responses to STS were mediated via endothelium-derived relaxing factors, CCRCs were performed in the absence or presence of the potassium channel inhibitors apamin (small-conductance, calcium-activated potassium channels, 100 nM) and TRAM-34 (intermediate-conductance, calcium-activated potassium channels, 10 μM) or the nitric oxide synthase inhibitor N-nitro-L-arginine methyl ester hydrochloride (l-NAME, 100 μM) or the cyclooxygenase inhibitor meclofenamate (1 μM).

*Statistical analysis.* Results are expressed as means ± SE. Two-way and one-way repeated-measures analysis of variance were used to compare differences in hemodynamic variables between groups and between different doses of STS and baseline, respectively. Friedman’s test was used to compare the differences for nonparametric variables. Student-Newman-Keul’s and Dunn’s test were used for post hoc analysis as appropriate. Regarding the in vitro vascular myography, the data are expressed as means ± SE of the negative log of the effective concentration (mol/l) that will give 50% of the maximum response (pEC50) or the maximum response (Emax). The significance of the difference between groups was determined by two-way ANOVA with Bonferroni’s posttest. Significance was defined as *P* < 0.05.

**RESULTS**

Comparing the control and STS-treated piglet groups, there were no significant differences in the age (2.6 ± 0.7 vs. 2.8 ±

![Graphs A-D](https://example.com/graphs.png)

**Fig. 2.** Cumulative dose effect of STS (●, *n* = 6) on cardiac index (A), common carotid artery flow index (CAFI; B), renal artery flow index (RAFI; C), and (D) superior mesenteric artery flow index (SMAFI; D) index compared with saline [control (○)]. *P* < 0.05 vs. controls (2-way ANOVA; *) and vs. baseline (1-way ANOVA; #).
0.4 days, respectively), weight (1.9 ± 0.1 vs. 2.2 ± 0.1 kg, respectively), blood gas, and hemodynamic measurements at baseline. The physiological and hemodynamic parameters of control piglets did not change significantly throughout the experimental period. The administration of STS did not affect the arterial blood gas measurements (P > 0.05 vs. baseline and the corresponding control values) (Table 1).

**STS does not cause significant systemic and pulmonary hemodynamic effects.** Intravenous administration of STS did not cause any significant changes in heart rate, CI, stroke volume, PAP, and estimated pulmonary vascular resistance index (VRI; Table 2 and Fig. 1). No episode of arrhythmia was identified during the administration of STS. STS at 30 mg/kg decreased MAP compared with baseline (P < 0.05), leading to a higher PAP-to-MAP ratio; however, these changes were not significantly different from the corresponding control values. The systemic VRI of piglets treated with STS at 3, 10, and 30 mg/kg and those corresponding systemic VRI of controls were lower than the respective baseline (both P < 0.05), with no difference between the two groups (P > 0.05).

**STS selectively increases mesenteric hemodynamic parameters.** SMA flow increased in a dose-dependent fashion in STS-treated piglets (P < 0.05) and became significantly higher than the baseline value at 3, 10, and 30 mg/kg (38 ± 4, 44 ± 4, and 52 ± 5 vs. 31 ± 5 ml·kg⁻¹·min⁻¹ of baseline, respectively; P < 0.05) (Fig. 2). There were no significant changes in common carotid and renal arterial flows with STS (0.1–30 mg/kg) administration.

**Effects of STS on systemic and regional oxygen transport.** Corresponding to the changes in SMA flow, the SMA oxygen delivery was significantly increased when STS at 3, 10, and 30 mg/kg was given (0.43 ± 0.06, 0.46 ± 0.08, and 0.49 ± 0.07 vs. 0.31 ± 0.01 ml O₂·min⁻¹·kg⁻¹ of baseline, respectively) (Fig. 3). STS did not cause any significant change in systemic, common carotid, and renal arterial oxygen delivery. There were no significant differences in systemic oxygen consumption and extraction ratio in the STS-treated group compared with the respective baseline and corresponding control values (data not shown).

**In vitro vascular myography in mesenteric and carotid arteries.** STS caused a concentration-dependent vasodilation in small mesenteric arteries (pEC₅₀ = 4.4 ± 0.04, E₉₉ = 99.1 ± 0.9% relaxation) but not in carotid arteries (Fig. 4). Vasodilation in mesenteric arteries was inhibited by a combination of potassium channel blockers (apamin, 100 nM and TRAM-34, 10 μM) causing a rightward shift of the STS response (pEC₅₀ = 4.0 ± 0.06,
DISCUSSION

To the best of our knowledge, this is the first study to investigate the systemic, pulmonary, and regional hemodynamic effects of intravenous administration of STS in healthy newborn subjects. Even though Danshen has been widely used in traditional Chinese medicine for various cardiovascular diseases (6, 11, 35), little is known about its hemodynamic effects, which is important in translational research. In this study, we demonstrated that intravenous STS dose-dependently increased SMA blood flow and oxygen delivery, without significant systemic, pulmonary, carotid, and renal hemodynamic effects except at the highest studied dosage of 30 mg/kg in newborn piglets. Interestingly, the mechanism for vasorelaxation does not rely on nitric oxide, and this could be important in states of oxidative stress where nitric oxide could be detrimental.

In part, similar to a previous report that purified tanshinones from Danshen caused in vitro vasodilatation of mesenteric, renal, and femoral arteries in adult rats and rabbits (20), we also observed that STS dose-dependently increased SMA blood flow in newborn piglets. However, the vasodilatory effect of STS appears to be tissue specific, since no significant vascular changes in the carotid and renal circulations were observed after receiving the similar dosage range of STS. Corresponding to dose-dependent changes in blood flow, SMA oxygen delivery was increased with STS administration.

NEC is the leading cause of death and long-term disability from gastrointestinal disease in preterm infants and is characterized by acute and chronic intestinal inflammation that may lead to systemic sepsis and multisystem organ failure (19, 22). Because ischemia is one of the pathophysiological factors for NEC in asphyxiated term neonates (12, 23), the improvement of mesenteric perfusion with STS infusion could be beneficial to neonates who are at risk for ischemic intestinal injury. By reducing leukocyte adhesion and scavenging oxygen-free radicals, it has also been shown recently that injection of Danshen extract can improve endotoxin-induced microcirculatory disturbance in rat mesentery (11). In view of the fact that minimal side effects have been observed in the current study, further investigations are thus worthwhile to examine this possibility of employing STS as a pharmacological therapy for treating or preventing NEC in critically ill neonates.

To further delineate the underlying mechanisms for vasorelaxant effects of STS, in vitro vascular myography was also carried out to compare its effect on rat mesenteric (resistance) and carotid (conduct) arteries. Despite differences in species (pigs vs. rats) and age (newborn vs. adult), STS also selectively caused a concentration-dependent vasodilation in SMA, but not carotid, artery. Although vasodilators such as acetylcholine are commonly mediated by a combination of nitric oxide, prostaglandins, and endothelium-derived hyperpolarizing factor, STS responses were not mediated by either nitric oxide or prostaglandins. Our findings further suggest that either STS is acting through a very specific, potassium channel-dependent pathway or through an as yet undetermined additional mechanism. Indeed, we believe that STS is likely causing a vasodilator response via the activation of endothelial potassium channels. STS has previously been shown to activate calcium-activated potassium channels in coronary arteries (33). The inhibitors of endothelial intermediate- and small-conductance
calcium-activated potassium channels (TRAM-34 and apamin, respectively) used in this study are commonly accepted to be synonymous with inhibition of endothelial-derived hyperpolarizing factor-mediated vasodilation. Activation of these channels causes hyperpolarization of the endothelial cell membrane, which is then transmitted to the smooth muscle cell to cause relaxation. Similarly, it has been shown that the vasodilatory effect of Danshen extract on rat isolated femoral artery was only blocked by a nonselective potassium channel blocker, but not by various receptor blockers or adenyllyl and guanylyl cyclase inhibitors (18). Contrary to our observation that endogenous nitric oxide may not be involved in STS-induced vasorelaxation, several in vitro (14, 17) and in vivo (15) studies have shown that Danshen and its extract caused vasodilation mainly by increasing nitric oxide production in chronic studies. Other than the differences in extract components used in the studies, the discrepancy may also be due to tissue specificity. It has been shown from the same research group that the vasodilatory effect of Danshen extract on knee joint blood vessel (17), but not femoral artery (18), was blocked by nitric oxide synthase inhibitor. Other potential mechanisms of the effect of Tanshinone IIA on blood flow include the regulation of phospholipase A$_2$ (31) and the activation of estrogen receptors (8).

In contrast to a previous study in albino rats and rabbits showing that Danshen significantly decreased systemic blood pressure (20), we observed a decrease in MAP only after treating the piglets with the highest dose of STS (30 mg/kg). However, it is worth noting that STS has recently been shown to reduce MAP only in hypertensive, but not healthy sham-operated, hamsters (15). As indicated by the corresponding decreases in systemic VRI, it is most likely that the decrease in blood pressure resulted from systemic vasodilatation (20). In view of the fact that initial hyperemia following hypoxia or ischemia represents a prerequisite to neuronal functional recovery (10), the vasodilating effect of STS could be beneficial to improve recovery from asphyxia.

The systemic vascular effect of STS may have interesting implications. As shown in Table 2, STS caused a dose-related increase in the PAP-to-MAP ratio, which was significantly higher than the baseline value at 30 mg/kg, in the absence of any significant changes in PAP. We do not know the significance of this increase in the ratio by ~50% from the baseline. This elevation might not be clinically relevant, since the ratio was still below 1.0: an equivalent or suprasystemic ratio. This elevation might not be clinically relevant, since the ratio did not observe any significant effect of STS on heart rate, CI, and stroke volume during the experimental period in these healthy newborn piglets.

In summary, intravenous administration of STS may be potentially beneficial in improving intestinal perfusion, which is likely dependent on the endothelium-derived hyperpolarizing factor but not nitric oxide pathway. Intravenous STS does not affect overall hemodynamics on newborn piglets at a dose range of 0.1–1 mg/kg. Further studies are required to demonstrate the effectiveness of STS as a therapeutic agent for NEC in newborn subjects.

ACKNOWLEDGMENTS

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GRANTS

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REFERENCES


