Role of Thromboxane A$_2$ in the Control of Myocardial O$_2$ Supply/Consumption Balance and Severity of Ischemia During Pacing-Induced Ischemia

Gary J. Grover and Charles S. Parham

The role of thromboxane A$_2$ (TXA$_2$) in the control of O$_2$ supply/consumption variables during pacing-induced ischemia was examined using the TXA$_2$ receptor antagonist SQ 29,548. Anesthetized, open-chest dogs were subjected to left anterior descending coronary artery (LAD) stenosis that produced significant epicardial S-T segment elevation (12 mV) only when superimposed on atrial pacing. Regional myocardial blood flow was determined using radioactive microspheres, and O$_2$ consumption was determined by measuring O$_2$ saturation of venous blood draining the ischemic region. The dogs were treated with saline or 0.2 mg/kg+0.2 mg/kg/hr SQ 29,548, and the effect on ischemia was determined during 5-minute pacing-induced ischemic episodes at 10, 40, and 70 minutes postdrug or saline treatment. SQ 29,548 significantly reduced S-T elevation at 40 and 70 minutes postdrug compared with saline values and at all times measured compared with its paired predrug pace+stenosis values. SQ 29,548 reduced S-T elevation approximately 45% compared with its paired predrug values at 70 minutes. SQ 29,548 resulted in a significantly higher subendocardial-to-subepicardial flow ratio (0.70±0.10, p<0.05) compared with saline-treated animals (0.42±0.06), with an overall increase of flow to the ischemic region of approximately 40%. This increased flow was matched by a proportional increase in O$_2$ consumption without a change in O$_2$ extraction. The O$_2$ supply/consumption balance was also unchanged by SQ 29,548 implying that despite the increase in blood flow, the ischemic region was still flow-limited. Thus, SQ 29,548 significantly reduced S-T elevation during pacing-induced ischemia, and this may be due in part to an improved subendocardial flow. (Circulation Research 1989;64:575-582)

Thromboxane A$_2$ (TXA$_2$) is a potent vasoconstrictor and platelet aggregating agent. This compound is known to be released during various pathological events, including myocardial ischemia. TXA$_2$ release during myocardial ischemia may further aggravate the ischemic conditions due to its constrictor and proaggregatory effects. Inhibition of TXA$_2$ synthetase or specific blockade of TXA$_2$ receptors appears to be efficacious in reducing the severity of ischemia, though little is known about the physiological mechanisms by which these compounds work.

Most of the studies on the effects of TXA$_2$ on myocardial ischemia were performed in models of ischemia of sufficient severity to result in infarction. TXA$_2$ has also been shown to be released during anginal attacks, though few studies have been performed with compounds inhibiting TXA$_2$ production or its action in models of stable angina pectoris. Studies have been performed in models of coronary cyclic flow variation (model of some aspects of unstable angina) where SQ 29,548 was shown to significantly reduce such flow reductions. TXA$_2$ synthetase inhibitors and receptor antagonists have yielded mixed results in angina patients, and we need to learn more about the effects of these compounds in models mimicking stable angina pectoris. One goal of the present study was to determine if the selective TXA$_2$/prostaglandin endoperoxide receptor antagonist SQ 29,548 can reduce the severity of ischemia in a model of pacing-induced ischemia where spontaneous flow variations are not observed. Since many antianginal agents have their effects via improvements in the O$_2$ supply/consumption balance, the second goal of this study was to determine if SQ 29,548 can reduce the severity of formation.
pacing-induced ischemia via effects on regional blood flow or \( O_2 \) consumption. This study was the first to determine the effect of TXA\(_2\) antagonism on regional \( O_2 \) supply/consumption variables in the ischemic heart.

**Materials and Methods**

**Surgical Procedure**

Mongrel dogs of either sex weighing between 10 and 16 kg were anesthetized with sodium pentobarbital (30 mg/kg i.v.). Aortic blood pressure was measured by using a Mikro-Tip catheter transducer (Millar Instruments, Houston, Texas) passed through the left femoral artery to the aorta. All recordings were made on a Grass Model 7D polygraph (Quincy, Massachusetts). A catheter was introduced into the right femoral vein, and sodium pentobarbital was infused at a rate of 0.1 mg/kg/min during the entire course of the experiment. Arterial blood was sampled via a right femoral arterial catheter for blood gas determination using an ABL3 blood gas analyzer (Radiometer, Copenhagen, Denmark).

Each dog was intubated and ventilated with room air using a respirator such that eucapnia was maintained. A left thoracotomy was performed at the fifth intercostal space, and a pericardial cradle was formed. A portion of the left anterior descending coronary artery (LAD) was isolated above the first branch, and a screw-type occluder was placed around the LAD. The myocardial ischemic changes were determined by six monopolar epicardial leads embedded 1 cm apart on a 4.5x3 cm silicone rubber patch sutured to the anterior surface of the left ventricle supplied by the LAD. The leads from each electrode were connected to a selector box that allowed rapid individual sampling of all sites. The epicardial electrocardiograms were recorded using the unipolar lead of a standard ECG amplifier and displayed on an oscilloscope. A bipolar pacing catheter was positioned in the right atrium close to the SA node and the stimulus artifact was superimposed over the P wave of the ECG. Atrial pacing was accomplished with a Grass stimulator (model S4G). S-T segment elevation was determined as the maximum deflection above the isoelectric point in the S-T interval.

A catheter was introduced into the left atrial appendage for injection of radioactive microspheres for the determination of myocardial blood flow. We used a reference flow method employing \(^{141}\text{Ce}, \^{51}\text{Cr}, \^{46}\text{Sc}, \) and \(^{85}\text{Sr}\)-labelled microspheres (15±3 \( \mu \)m; 3M Co, St. Paul, Minnesota). For the flow determination, \( 3x10^6 \) microspheres were shaken for several minutes and injected as a 0.5-ml bolus into the atrial catheter followed by a 2–3 ml saline flush. A femoral arterial blood sample was obtained with a peristaltic pump set at a fixed rate (5 ml/min). Withdrawal was begun 30 seconds before injection of microspheres and was continued for a total of 2 minutes. At the end of the experiment, multiple transmural tissue samples (0.4–0.6 g) were removed from the nonischemic tissue and from the ischemic tissue under the epicardial ECG leads. These samples were divided into subepicardial and subendocardial halves and were tested for radioactivity along with the reference blood samples in a gamma counter (Gamma 8000, Beckman, Fullerton, California). Total ischemic and nonischemic regional flows were calculated as milliliters per minute per 100 g. Ischemic regional \( O_2 \) consumption was determined via a venous catheter (left interventricular vein) that collected blood from the LAD perfused region as described previously. The catheter was allowed to drain throughout the experiment, and samples were collected anaerobically and passively into a 1-ml syringe. This venous sample, as well as an arterial blood sample, were tested for hemoglobin (Hb) and \( O_2 \) saturation (SaO\(_2\), SvO\(_2\)) with a Radiometer OSM-2 hemoximeter. \( O_2 \) content (CaO\(_2\), CvO\(_2\)) was calculated by multiplying the \( O_2 \) saturation by the Hb concentration by 1.36. \( O_2 \) consumption was then calculated from \( (\text{CaO}_2 - \text{CvO}_2) \times \text{MBF} \); where MBF equals mean myocardial blood flow (microspheres) in the LAD region (milliliters per minute per 100 g). The \( O_2 \) supply/consumption ratio was calculated from

\[
\frac{\text{CaO}_2 \times \text{MBF}}{(\text{CaO}_2 - \text{CvO}_2) \times \text{MBF}}
\]

which reduces to

\[
\frac{\text{SaO}_2}{(\text{SaO}_2 - \text{SvO}_2)}.
\]

**Experimental Protocol**

A stabilization period was followed by measurement of control responses of all the hemodynamic, blood flow, and \( O_2 \) parameters, including surface mapping of epicardial ECGs. Measurements were then made in the presence of pacing performed for 5 minutes at 70–80 beats/min above baseline heart rate. Then brief periods (<2 minutes) of pacing were accompanied by gradual reduction in the LAD flow with the screw clamp until significant (12 mV) S-T segment elevation was recorded in the ischemic area. This level of constriction was accepted if the ECG changes (mean of all leads) disappeared after the pacing was discontinued and could be reproduced with renewed pacing. The LAD stenosis was then maintained throughout the rest of the experiment. Once these criteria were met, at least 10 minutes were given to allow the preparation to stabilize. Hemodynamic variables and epicardial mapping were always measured between 4–5 minutes into pacing. The animals were then divided into the following groups: Group 1 consisted of intravenous saline-treated controls (n=7). Saline was infused over a 10-minute period (4.5 ml total) and a subsequent infusion of 2 ml/hr throughout the experiment. Group 2 consisted of intravenous SQ 29,548-treated animals (n=8). SQ 29,548 was infused at a dose of 0.2 mg/kg+0.2 mg/kg/hr throughout the experiment.
TABLE 1. Effect of Saline or SQ 29,548 on Hemodynamic and Blood Gas Variables During Pacing-Induced Ischemia

<table>
<thead>
<tr>
<th></th>
<th>Prepacing</th>
<th>Pacing</th>
<th>Pacing+stenosis (Minutes postdrug or saline)</th>
<th>Stenosis (recovery)</th>
<th>Predrug</th>
<th>Postdrug</th>
<th>10</th>
<th>40</th>
<th>70</th>
<th>10</th>
<th>40</th>
<th>70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline (n=7)</td>
<td>116±6</td>
<td>113±6</td>
<td>118±5</td>
<td>116±6</td>
<td>118±8</td>
<td>118±7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SQ 29,548 (n=8)</td>
<td>121±10</td>
<td>118±11</td>
<td>129±10</td>
<td>130±8</td>
<td>132±7</td>
<td>136±10</td>
<td>135±8</td>
<td>133±7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline (n=7)</td>
<td>88±5</td>
<td>89±6</td>
<td>90±5</td>
<td>87±7</td>
<td>90±8</td>
<td>87±8</td>
<td>83±14</td>
<td>88±8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SQ 29,548 (n=8)</td>
<td>93±9</td>
<td>92±11</td>
<td>101±10</td>
<td>99±8</td>
<td>99±9</td>
<td>104±10</td>
<td>101±9</td>
<td>103±7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline (n=7)</td>
<td>148±9</td>
<td>227±7*</td>
<td>227±7*</td>
<td>151±9</td>
<td>149±8</td>
<td>227±7*</td>
<td>227±7*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SQ 29,548 (n=8)</td>
<td>154±5</td>
<td>232±4*</td>
<td>232±4*</td>
<td>154±5</td>
<td>154±6</td>
<td>232±4*</td>
<td>232±4*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PacO2 (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline (n=7)</td>
<td>81±4</td>
<td>81±4</td>
<td>83±4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SQ 29,548 (n=8)</td>
<td>86±4</td>
<td>86±4</td>
<td>81±4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaCO2 (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline (n=7)</td>
<td>38±1</td>
<td>38±1</td>
<td>38±1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SQ 29,548 (n=8)</td>
<td>37±1</td>
<td>37±1</td>
<td>38±1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline</td>
<td>7.38±0.2</td>
<td>7.38±0.2</td>
<td>7.37±0.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SQ 29,548</td>
<td>7.37±0.3</td>
<td>7.36±0.3</td>
<td>7.37±0.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All values are mean±SEM. *Significantly different from its paired prepaced value (p<0.05).

After drug administration each successive 5-minute pacing episode was performed at 10, 40, and 70 minutes after the onset of drug treatment. After each pacing episode, the S-T segment elevation was seen to return to baseline or the animal was not accepted. Blood gases and myocardial blood flows were determined during baseline conditions, pacing alone, pacing+LAD stenosis, and during pacing+LAD stenosis at 70 minutes postdrug or saline treatment. Overall ischemic region flows were determined from these measurements.

Statistics

All data are expressed as mean±SEM. Between-treatment (SQ 29,548 vs. vehicle) comparisons were made using a Student's t test. Within treatment comparisons (changes with time) were made using a randomized block ANOVA for all physiological variables measured. A Newman-Keuls test was used for multiple comparisons. Comparisons of percent changes (percent change in S-T elevation, blood flow, and O2 consumption) were made using the Mann-Whitney U test for nonparametric data. A value of p<0.05 was accepted as significant.

Results

Hemodynamic and blood gas data for saline- and SQ 29,548-treated animals are shown in Table 1. No marked changes in systolic or diastolic blood pressure were observed within or between treatments at any time measured. Pacing was adjusted so that heart rate was elevated 70–80 beats/min above baseline levels. Blood gases were held constant throughout the experiment. The effect of saline or randomized block ANOVA for all physiological variables measured. A Newman-Keuls test was used for multiple comparisons. Comparisons of percent changes (percent change in S-T elevation, blood flow, and O2 consumption) were made using the Mann-Whitney U test for nonparametric data. A value of p<0.05 was accepted as significant.

TABLE 2. Effect of Saline or SQ 29,548 on S-T Segment Elevation During Pacing-Induced Ischemia

<table>
<thead>
<tr>
<th></th>
<th>Prepacing</th>
<th>Pacing</th>
<th>Pacing+stenosis (Minutes postdrug or saline)</th>
<th>Stenosis (recovery)</th>
<th>Predrug</th>
<th>Postdrug</th>
<th>10</th>
<th>40</th>
<th>70</th>
<th>10</th>
<th>40</th>
<th>70</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-T segment elevation (mV)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline (n=7)</td>
<td>1.1±0.2</td>
<td>1.1±0.5</td>
<td>11.8±0.9*</td>
<td>9.4±1.6*</td>
<td>2.1±0.4</td>
<td>12.0±1.3*</td>
<td>1.8±0.5</td>
<td>11.9±1.0*</td>
<td>2.4±1.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SQ 29,548 (n=8)</td>
<td>0.9±0.1</td>
<td>1.0±0.2</td>
<td>12.4±0.8*</td>
<td>8.2±1.5†</td>
<td>1.9±0.7</td>
<td>7.8±1.4††</td>
<td>1.7±0.9</td>
<td>6.6±1.4††</td>
<td>1.8±0.9</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All values are mean±SEM.

*Significantly different from its paired prepaced value (p<0.05).
†Significantly different from pre-drug pace+stenosis value (p<0.05).
‡Significantly different from its respective saline group value (p<0.05).
drug treatment on epicardial S-T segment elevation during pacing-induced ischemia is shown in Table 2. Pacing alone did not significantly elevate the S-T segment, however when LAD stenosis was superimposed on pacing, significant S-T segment elevation occurred. The S-T elevation observed during predrug pacing-induced ischemia was similar in both groups of animals meaning that these groups were exposed to ischemia of approximately similar severity. Upon cessation of pacing, the S-T segment returned to control levels despite the existing coronary stenosis. After saline treatment, the S-T elevation observed during subsequent episodes of pacing-induced ischemia did not significantly change from presaline ischemic values. Treatment with SQ 29,548 resulted in significant decreases in pacing-induced S-T elevation compared with the respective saline group values at 40 and 70 minutes postdrug treatment. When compared with their own paired predrug pacing+stenosis values, SQ 29,548 significantly reduced S-T segment elevation at all times measured. LAD blood flow (as measured using a flow probe) was measured throughout the experiment, and these data are shown on Table 3. No dramatic changes in LAD flow (slight changes were observed with pacing or LAD stenosis) occurred and cyclic flow variations were never observed in any experiment.

S-T segment data are expressed as a percent change from their predrug pacing-induced ischemia values on Figure 1. Treatment with SQ 29,548 resulted in a significant reduction in S-T elevation as a percent of its predrug values at 40 and 70 minutes postdrug treatment when compared with saline-treated animals. SQ 29,548 reduced S-T segment elevation approximately 40% at 40 minutes and 45% at 70 minutes postdrug. Saline-treated animals experienced a slight reduction in S-T segment elevation at 10 minutes posttreatment, but this returned to pretreatment values at the later measurement times. A representative trace from a drug-treated dog is shown in Figure 2. In this animal, the drug appeared to work only at the 70-minute point.

Regional myocardial blood flows and their transmural distributions are shown in Table 4. Pacing tended to slightly increase mean myocardial blood flow and slightly reduce the subendocardial-to-subepicardial (endo/epi) flow ratio. In the occluded LAD region, coronary stenosis during pacing tended to reduce flow to this region in both groups with a significant reduction in the endo/epi flow ratio being observed. At 70 minutes postsaline treatment, blood flow was slightly reduced compared with the corresponding presaline pace+stenosis value in the occluded region. The endo/epi flow ratio was also further reduced at 70 minutes in this group. SQ 29,548 treatment tended to result in an increased ischemic regional flow when compared with its predrug values: SQ 29,548 resulted in a 42±22% increase in flow which was significantly higher than the percent change in flow seen for saline-treated animals (-10±19%). Most of the flow increase with drug-treatment occurred in the subendocardial region as the endo/epi flow ratio in the ischemic region at 70 minutes post-SQ 29,548 treatment was significantly higher compared with the respective saline group value.

O₂ supply/consumption data are shown on Table 5. O₂ extraction (%) ranged between 60% and 70% in the LAD perfused region before ischemia or pacing and was similar in both groups. Pacing did not greatly affect extraction, but when LAD stenosis was superimposed on the pacing, O₂ extraction was significantly increased to similar levels in both

![Figure 1](http://circres.ahajournals.org/)

**Figure 1.** The effect of SQ 29,548 or saline on pacing-induced S-T segment elevation. This is expressed as the percent change in S-T elevation from predrug or vehicle pace+stenosis values. SQ 29,548 treatment (n=8) resulted in a significantly greater percent decrease in S-T elevation compared to saline treated controls (n=7) at 40 and 70 minutes posttreatment. *Significant difference from saline treated animals (p<0.05).
groups as the region became flow-limited. Treatment with SQ 29,548 did not result in a change in $O_2$ extraction at 70 minutes posttreatment. $O_2$ consumption increased slightly in both groups during pacing though LAD stenosis tended to reduce this to levels below prepaced baseline values. SQ 29,548 treatment significantly increased $O_2$ consumption 49±4% during pacing-induced ischemia compared to predrug pace+stenosis values versus a decrease of 9±15% for saline controls. $O_2$ consumption remained relatively constant during pacing-induced ischemia in saline-treated animals. The $O_2$ supply/consumption balance was similar in both groups under baseline conditions. This ratio decreased slightly with pacing, and when the LAD was stenosed during pacing, the ratio was significantly decreased in both groups compared with their prepaced baseline values. SQ 29,548 did not affect the $O_2$ supply/consumption ratio during pacing-induced ischemia when compared with saline values or with the paired predrug pace+stenosis values.

**Discussion**

$TXA_2$ has been shown to be released during myocardial ischemia in models of angina pectoris as well as during acute myocardial infarction.$^3,4,10,17$ Since $TXA_2$ has been found to aggregate platelets and contract coronary arteries it has been speculated that $TXA_2$ may exert a deleterious effect during ischemia. Studies using $TXA_2$ synthetase inhibitors have indicated that $TXA_2$ release during ischemia may indeed be harmful.$^5,6$ One problem with the use of $TXA_2$ synthetase inhibitors in determining the role of $TXA_2$ in ischemia is that these compounds may result in altered production of arachidonic acid metabolites from parallel pathways, thus clouding data interpretation.$^{18}$ Recently, selective $TXA_2$ receptor antagonists have been developed that allow the study of the effects of $TXA_2$ in a more direct fashion.$^{12}$ These compounds have been used in models of myocardial ischemia in rats and cats and have been efficacious in reducing the severity of some indexes of ischemia.$^9,19-21$ These studies were performed in models of total coronary occlusion of sufficient severity that infarct evolution was taking place. $TXA_2$ antagonists have also been effective in mitigating cyclic flow variations secondary to coronary endothelial damage and subsequent platelet aggregation.$^5,9,10$ A model probably resembling many aspects of unstable angina.

Few studies assessing the efficacy of $TXA_2$ receptor antagonists in models of stable angina pectoris

---

**TABLE 4. Effect of Saline or SQ 29,548 on Myocardial Blood Flow During Pacing-Induced Ischemia**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Nonoccluded region</th>
<th>Occluded region</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-pacing</td>
<td>Pacing+stenosis</td>
</tr>
<tr>
<td>Saline (n=7)</td>
<td>66±11</td>
<td>78±7</td>
</tr>
<tr>
<td>SQ 29,548 (n=7)</td>
<td>70±6</td>
<td>77±14</td>
</tr>
<tr>
<td>Endo/epi flow ratio</td>
<td>1.19±0.03</td>
<td>1.07±0.08</td>
</tr>
<tr>
<td>SQ 29,548 (n=7)</td>
<td>1.03±0.08</td>
<td>0.91±0.10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Prepacing+stenosis+drug (70 min postdrug or saline)</th>
<th>Prepacing+stenosis+drug (70 min postdrug or saline)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline (n=7)</td>
<td>124±20*</td>
<td>120±33</td>
</tr>
<tr>
<td>SQ 29,548 (n=7)</td>
<td>110±15*</td>
<td>123±18*</td>
</tr>
<tr>
<td>Endo/epi flow ratio</td>
<td>0.88±0.11</td>
<td>0.88±0.13</td>
</tr>
<tr>
<td>SQ 29,548 (n=7)</td>
<td>1.02±0.06</td>
<td>0.99±0.11</td>
</tr>
</tbody>
</table>

Endo/epi, endocardial-to-epicardial.

All values are mean±SEM.

*Significantly different from its respective prepaced value ($p<0.05$).
†Significantly different from its respective prepaced value ($p<0.05$).
‡Significantly different from its respective saline value ($p<0.05$).
have been performed. In models of cyclic flow variations, frank platelet aggregation and activation would make TXA2 antagonists obvious choices as agents which may mitigate such aggregation because of the important role of TXA2 in such models. The role of TXA2 in reversible effort induced ischemia is not quite so clear. Also, it should be pointed out that compounds that are effective in infarct models may not necessarily be effective in models of ischemia of lesser severity. For instance, compounds that mitigate the inflammatory response or affect neutrophil function may have a marked infarct-reducing effect but may not be beneficial in acute ischemic episodes of insufficient severity to result in an inflammatory response but of sufficient severity to result in symptoms such as chest pain. Most compounds which are effective antianginal agents are ones that seem to have an effect on the O2 supply/consumption balance in the ischemic myocardium.11,14 TXA2 is known to be released during ischemic conditions like angina, though it is unknown if this release can initiate or aggravate the ischemia.3 Unfortunately, TXA2 inhibitors and receptor antagonists have shown mixed results in a few clinical and experimental studies on angina pectoris.10,11,19 In the present study, we determined the effect of the selective TXA2/prostaglandin endoperoxide receptor antagonist SQ 29,548 in a model of pacing-induced ischemia mimicking effort-induced angina. In this study, we determined not only the effect of this compound on epicardial S-T elevation during pacing-induced ischemia but also how it affects myocardial O2 supply/consumption variables.

The model used in this study was pacing-induced ischemia, which is similar in many ways to effort-induced angina. Similar models have been used previously.22 In our model, LAD stenosis by itself did not result in significant ischemia as judged by S-T segment elevation, but upon pacing, a significant S-T elevation was observed. With cessation of pacing, the S-T elevation always returned to baseline values, and this "reversible" ischemia was relatively easy to attain. It should be noted that during the experiment our index of severity of ischemia was S-T elevation. We did not occlude the LAD by a prescribed degree because of the extreme variability in S-T segment elevation and tissue flows (microspheres) obtained by this method. S-T segment elevation has been shown to be well correlated with ischemic regional blood flow and severity of ischemia23 and in our study, predrug microsphere flows during pacing+stenosis in the ischemic region were nearly identical in the two groups when their S-T elevations were maintained at similar levels. S-T segment shifts have been found to correlate well with flow as well as myocardial metabolic changes associated with ischemia, such as lactate extraction decreases and potassium effects.24,25 Karlsson et al26 found that S-T elevation was correlated with depletion of ATP and creatine phosphate. Thus, S-T elevation in this model was useful for determining acute severity of ischemia particularly when coupled with flow and O2 measurements. It also is important to note that no cyclic flow reductions were observed throughout the experiment and that S-T elevation returned to baseline levels immediately upon cessation of pacing. This indicates that large scale platelet aggregation was not evident at the site of stenosis. This still does not rule out a more subtle role for platelets in this model, and more work is warranted.

S-T elevation was reduced in SQ 29,548-treated animals compared with the saline group only at the 40- and 70-minute postdrug time periods. Why SQ 29,548 had greater benefit during the later ischemic episodes is unknown. Previous studies have shown that the dose of SQ 29,548 used in this study blocks >99% of the femoral vascular TXA2 receptors as early as 10 minutes postdrug.21 It is possible that at 10 minutes, penetration of the drug into the myocardium was incomplete. It is also possible that the elicitation or mediation of pathological events by TXA2 is of greater importance in later ischemic episodes.
We also examined the effects of SQ 29,548 on the ischemic regional O\textsubscript{2} supply/consumption balance. Pacing during LAD stenosis resulted in <50% reduction of myocardial flow with the subendocardial flow being the most compromised. SQ 29,548 significantly improved subendocardial flow during pacing-induced ischemia, and this may be one mechanism for its beneficial action. Flow probe flows were not normalized for tissue mass and were thus not used for determining blood flow effects of SQ 29,548. Other antianginal compounds are thought to be effective due, in part, to their beneficial effects on subendocardial blood flow.\textsuperscript{2,27} SQ 29,548 did not seem to have a major effect on nonischemic flow or its regional distribution, suggesting that it is not a nonselective vasodilator. TXA\textsubscript{2} is known to be a coronary constrictor, though it is not particularly potent in adult canine coronary arteries relative to other species.\textsuperscript{2} The effect of TXA\textsubscript{2} or mimetics on regional flow distribution is not clear at this time.

O\textsubscript{2} consumption and extraction values in the LAD perfused region were in the range reported in previous studies.\textsuperscript{13,28} SQ 29,548 treatment resulted in a significant percent increase in ischemic regional O\textsubscript{2} consumption from predrug values compared with saline-treated animals. This increased O\textsubscript{2} consumption was probably due to the increased O\textsubscript{2} delivery to the subendocardial region in SQ 29,548-treated animals. Unfortunately, we could not measure subendocardial O\textsubscript{2} consumption with the techniques used in this study. It appears that the O\textsubscript{2} consumption with SQ 29,548 treatment increased in a fashion proportional to the increase in blood flow, since the O\textsubscript{2} supply/consumption balance as well as O\textsubscript{2} extraction remained unchanged in the ischemic region. This implies that the ischemic region was still flow-limited, though the increased flow was evidently sufficient to result in some relief from the symptoms of the ischemia. Agents that can improve relative subendocardial flow (such as nitroglycerin) have been shown to also improve the subendocardial O\textsubscript{2} supply/consumption balance, though this was measured using techniques such as microspectrophotometry where regional O\textsubscript{2} (subepicardial, subendocardial) saturation can be reliably measured.\textsuperscript{13} Subendocardial improvements in oxygenation may have existed in this study, but our technique of measuring overall ischemic regional O\textsubscript{2} saturation may not have been sensitive enough to record this activity. SQ 29,548 may have selectively improved subendocardial flow since this was the most ischemic region and may have been producing relatively high levels of TXA\textsubscript{2}.

Thus, TXA\textsubscript{2} release does appear to mediate some of the pathological events seen during pacing-induced ischemia, a potentially useful model of effort-induced angina pectoris. SQ 29,548 was efficacious in reducing the severity of this pacing-induced ischemia because S-T elevation was reduced 40–50%. Subendocardial flow was improved, though the exact contribution of this to the antiischemic effects of SQ 29,548 is still unknown.

References


**KEY WORDS** • O2 consumption • myocardial ischemia • SQ 29,548 • blood flow
Role of thromboxane A2 in the control of myocardial O2 supply/consumption balance and severity of ischemia during pacing-induced ischemia.

G J Grover and C S Parham

Circ Res. 1989;64:575-582
doi: 10.1161/01.RES.64.3.575

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1989 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/64/3/575

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/