Effects of Thiopental on Regional Blood Flows in the Rat

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Background: The goal of this investigation was to characterize the effects of thiopental on cardiac output and regional blood flows in the rat. Blood flows influence thiopental pharmacokinetics. Acquisition of these data may ultimately permit evaluation of the contribution of thiopental-induced alterations in regional blood flows to the disposition and hypnotic effect of this drug.

Methods: Chronically instrumented unrestrained Wistar rats (n = 20) aged 3–4 months received either a dose of thiopental sufficient to induce a brief period of unconsciousness (20 mg·kg−1) or a larger dose achieving electroencephalographic burst suppression (45 mg·kg−1). Cardiac output and blood flows to 14 tissues were determined at 4 times in each rat for a period of 420 min using injections of radioactive microspheres (expressed as mean ± SD). Mean arterial pressure, heart rate, and blood gas tensions were determined at all measurement times. Arterial plasma concentrations were sampled at postinjection times.

Results: No important changes in systemic cardiovascular measurements were detected after the smaller dose of thiopental. One minute after the larger dose, cardiac output decreased from baseline (123 ± 14 vs. 84 ± 11 ml·min−1, P < 0.01), flow to muscle and fat decreased, and muscle and fat resistance increased. At 5 min, compared to baseline, no difference in cardiac output was detected (123 ± 14 vs. 119 ± 11 ml·min−1), intestinal flows increased, and intestinal resistances decreased. Cardiac output was again depressed at 30, 90, and 180 min. Brain blood flow decreased 25 ± 19% (P < 0.01) from baseline for the duration of the study.

Conclusions: Thiopental acutely decreases cardiac output, and blood flows to muscle and fat tissue. The temporary return of cardiac output to baseline may be related to intestinal vasodilation. These blood flow alterations may influence the pharmacokinetics of thiopental. (Key words: Anesthetics, intravenous thiopental. Animals: rat. Drug effects: regional blood flows. Hemodynamics: drug effects.)

CARDIAC output and regional blood flows transport thiopental to the central nervous system and distribute it to body tissues. The dose of thiopental required to cause patients to drop a held syringe or to achieve 3–5 s of isoelectric electroencephalogram has been shown to be positively correlated with cardiac output.1 However, thiopental itself can cause significant depression in cardiac output. The influence of thiopental-induced alterations in regional blood flows on thiopental pharmacokinetics has not been determined.

Organs and tissues of kinetic importance are the brain, the organ of intended pharmacologic effect, the liver and kidney, the organs of metabolism and excretion, and muscle and fat, the tissues of distribution. There are a few studies of thiopental's steady-state effects on blood flows to most of the aforementioned important organs.2–4 Acute blood flow versus time responses to thiopental are reported for individual organs,5,6 but not for all organs simultaneously and not for the tissues of distribution. The goal of the current study is to quantitate in rats the time course of cardiac output and regional blood flows after thiopental administration. In future analyses, blood flow data will be used to develop a physiologically based pharmacokinetic model describing thiopental uptake into multiple organs and tissues.7 The model will be used to simulate the pharmacokinetic effect of thiopental-induced changes in blood flows.
Methods

The effects of thiopental on regional blood flows were determined in chronically instrumented rats using a radioactive microsphere technique. Rats were allowed to move freely and received 20 mg·kg⁻¹ or 45 mg·kg⁻¹ intravenous thiopental, respectively. We tested the null hypothesis that hemodynamics and regional blood flows do not change over time after intravenous bolus administration of thiopental.

Animals

Studies were performed in male Wistar rats (Harlan Sprague Dawley, Indianapolis, IN) weighing 401 ± 50 (SD) g and aged 3–4 months after approval of the animal care committees of the Palo Alto Veterans Administration Hospital and Stanford University Medical Center. All rats were housed individually for at least 2 weeks at the Veterans Administration animal facility, fed rat chow, watered ad libitum, and maintained at 22–23°C with a 12-h light-dark cycle.

Surgery for Chronic Instrumentation

Two days before the microsphere studies, catheters were placed in the left ventricle, the superior vena cava, and the aorta under isoflurane-oxygen anesthesia. Tapered PE-50 polyethylene tubing was inserted via the right carotid artery into the left ventricle for microsphere injections, and position was confirmed by pressure measurement. One end of PE-10 tubing was glued inside one end of PE-50 tubing, and threaded through the right jugular vein 0.5 cm above the right atrium for drug infusion. The femoral artery was cannulated with tapered PE-50 tubing, and the catheter was advanced into the abdominal aorta 0.5 cm from the bifurcation of the iliac arteries and used for arterial blood sampling and hemodynamic measurements. All catheters were tunneled subcutaneously and brought to the surface at the nape of the neck.

Radioactive Microsphere Method

In brief, gamma-labeled 15 μm diameter spherical resins (New England Nuclear, Boston, MA) were injected into the ventricular catheter. The microspheres mixed with blood in the left ventricle and were entrapped in the first pass through tissue vasculature in direct proportion to the blood flow to that tissue. The number of spheres in an arterial sample drawn during microsphere distribution was used as a reference to determine cardiac output and absolute regional blood flows. Administering spheres with different labels enabled multiple blood flow determinations in a single rat.

One day before each study, vials of microspheres in saline were placed in an ultrasonic bath for at least 10 min. and approximately 65,000 microspheres in 0.2 ml were drawn into polyethylene tubes coiled about a syringe casing and counted. On the day of the study, the tubes were agitated just before injection, and administered smoothly into the left ventricle over 10 s followed by a 0.5-ml saline flush over the succeeding 15 s. Ten seconds before and sixty seconds after the microsphere injection, reference arterial blood was withdrawn at 0.63 ml·min⁻¹ using an infusion-withdrawal pump (Model 907, Harvard Bard, MA). Reference blood was replaced with equal blood volumes from donor rats. After the last microsphere injection, rats were killed by decapitation and the following organs were removed: lung, brain, heart, liver, left and right brain hemispheres, testes, left and right kidneys, pancreas, spleen, stomach, and large intestine. Aliquots of small intestine (6 g), perirenal fat (7 g), dorsal skin (15 g), and abdominal muscle (15 g) were obtained. The tissues were blotted on filter paper and weighed, and microsphere radioactivities were counted in a multichannel gamma counter (model 5230, Packard Autogamma Spectrometer), and separated using spectral deconvolution.

Blood flows were measured four times per rat using microspheres labeled with either ⁵⁷Co, ¹¹¹Sn, ⁸⁵Sr, or ⁴⁶Sc. Interference between the energy spectral peaks emitted by the isotopes constrained the number of measurements per rat.

Experimental Measurements

Mean arterial blood pressure and heart rate were monitored via the arterial catheter (Gb23R blood pressure transducer, Gould, Santa Clara, CA; Cardiomax II, Columbus Instruments, Columbus, OH). Plasma concentrations in 200 μl arterial blood were determined using a high-pressure liquid chromatographic method with ultraviolet detection. The lower limit of quantitation is less than 1 μg·ml⁻¹ in 50 μl plasma. The hematocrit of each blood sample was measured (2201 Micro-capillary reader, Damon/IEC, Needham, MA). Blood gas data were obtained from 20 μl arterial blood (178 pH/Blood Gas Analyzer, Ciba Corning, Medfield, MA).
Dose Selection

The two thiopental doses, henceforth referred to as the low (20 mg·kg⁻¹) and high (45 mg·kg⁻¹) doses, were selected to produce unconsciousness in a non-ventilated rat with minimal and maximal perturbations in heart rate and blood pressure. The high dose was sufficient to achieve electroencephalographic burst suppression.¹⁰

Experimental Protocols

The rats received 5–8 training sessions 45–60 min long on different days to accustom them to handling and study conditions. On the day of the study, the restrained rats were placed in a rodent sling suit (Harvard Instruments, Boston, MA) and the unrestrained rats were placed in experimental boxes (12" × 6" × 5"). The catheters were connected, and hemodynamics were allowed to equilibrate.

Control blood flows were measured approximately 5 min before thiopental administration. Either 20 or 45 mg·kg⁻¹ intravenous thiopental was administered tria infusion pump over 0.75 min. Postinfusion blood flows were measured in 10 rats at 1, 30, and 180 min (5 rats per dose), and in 10 rats at 5, 90, and 420 min (5 rats per dose). The measurement times were selected to cover the plasma pharmacokinetic profile in the rat.¹¹

The sequence for each postinfusion blood flow measurement was as follows: hemodynamic measurement, arterial sample for thiopental, microsphere procedure, arterial sample for thiopental, arterial sample for blood gas analysis, and hemodynamic measurement. The series of measurements requires approximately 3 min to complete. A thermal heating blanket was used to maintain rectal temperature near 38.1°C. The rats receiving the high dose were placed in a flow-through methyl methacrylate polymer box in 100% oxygen 15–30 s after starting the thiopental injection.

Calculations and Statistical Analyses

Tissue samples that received less than 200 microspheres were excluded from analysis. A minimum of 400 microspheres per sample was recommended on the basis of statistical theory and experiments in dogs.¹² However, we based our cutoff on a study in rats, where more than 200 microspheres per reference sample permitted quantitation of cardiac output within 10% of that measured by electromagnetic flow probe.¹³

Cardiac output was determined as cardiac output = injected microspheres × reference withdrawal rate ÷ microspheres in reference sample. Regional blood flows were calculated as \( Q_i = \text{microspheres in tissue sample} ÷ \text{sample mass} × \text{reference withdrawal rate} ÷ \text{microspheres in reference sample} \). Microspheres in the liver and lung were used to calculate hepatic artery and bronchial blood flows. To determine portal and total liver blood flows, absolute flows to splanchic organs were summed. Mass of the small intestine was assumed to be 3.5% of total body weight.¹⁴ Systemic and organ resistances were computed as the ratio of mean arterial pressure to blood flow. Vascular resistances in preportal organs were calculated assuming a portal venous pressure of 9 mmHg.¹⁴

Blood flows and vascular resistances were examined within dose groups for time effects by analysis of variance. If differences were detected, flows were compared with control using Dunnett’s multiple comparison test.

All results are reported as mean ± standard deviation. Statistical significance was accepted when the null hypothesis had a probability of less than 5% (P < 0.05). All statistical analyses were done with MATLAB (The Mathworks, Natick MA).

Results

Table 1 demonstrates cardiovascular depression in the rats receiving the high dose, and to a much lesser degree in the rats receiving the low dose. The high dose of thiopental depressed cardiac output at 1, 30, 90, and 180 min, and mean arterial pressure and heart rate at 1, 5, and 30 min. Systemic vascular resistance increased at 1 min, then decreased at 5 min. Our general impression is that the cardiovascular system is depressed between 1–180 min with a momentary return in cardiac output toward baseline at 5 min.

Table 2 describes the ventilatory depression that occurred after administration of the high dose. Arterial carbon dioxide partial pressure increased from control throughout the entire experiment, and pH is depressed between 1 and 180 min. The rats receiving the low dose had an isolated increase in \( P_{\text{aCO}_2} \), at 1 min. The dose difference in oxygen partial pressure is caused by the supplemental oxygen used in the high dose group. Plasma concentrations decline to 50% of initial values by 5 min for both doses. The ratio between the average concentrations for each dose group is 2.4 at 1 min and 5.5 at 420 min, suggesting nonlinear pharmacokinetics.

Figure 1 depicts rapid thiopental-induced depression in regional blood flows to fat and muscle after the high dose. Blood flow decreased at 1 min in muscle (13 ±
### Table 1. Temporal Effects of Thiopental on Total Body Hemodynamics

<table>
<thead>
<tr>
<th>Measurement Time (min)</th>
<th>Baseline</th>
<th>1</th>
<th>5</th>
<th>30</th>
<th>90</th>
<th>180</th>
<th>420</th>
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<tbody>
<tr>
<td><strong>CO (ml·min⁻¹)</strong></td>
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<tr>
<td>Low dose</td>
<td>125 ± 23</td>
<td>104 ± 9</td>
<td>109 ± 12</td>
<td>109 ± 6</td>
<td>106 ± 17</td>
<td>122 ± 19</td>
<td>99 ± 23</td>
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<td>High dose*</td>
<td>123 ± 14</td>
<td>84 ± 11‡</td>
<td>119 ± 11</td>
<td>97 ± 12§</td>
<td>102 ± 8‡</td>
<td>92 ± 7‡</td>
<td>120 ± 31</td>
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<td><strong>CI (ml·min⁻¹·kg⁻¹)</strong></td>
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<tr>
<td>Low dose†</td>
<td>302 ± 43</td>
<td>262 ± 40</td>
<td>259 ± 28</td>
<td>260 ± 17</td>
<td>255 ± 33§</td>
<td>300 ± 39</td>
<td>237 ± 45§</td>
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<tr>
<td>High dose*</td>
<td>311 ± 32</td>
<td>222 ± 35‡</td>
<td>291 ± 38</td>
<td>256 ± 32§</td>
<td>250 ± 16‡</td>
<td>242 ± 19‡</td>
<td>288 ± 41</td>
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<td><strong>MAP (mmHg)</strong></td>
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<tr>
<td>Low dose</td>
<td>100 ± 9</td>
<td>85 ± 13</td>
<td>93 ± 3</td>
<td>92 ± 3</td>
<td>98 ± 16</td>
<td>88 ± 8</td>
<td>97 ± 15</td>
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<tr>
<td>High dose*</td>
<td>107 ± 11</td>
<td>91 ± 7‡</td>
<td>79 ± 5‡</td>
<td>86 ± 11‡</td>
<td>100 ± 5</td>
<td>105 ± 10</td>
<td>101 ± 12</td>
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<tr>
<td><strong>HR (min⁻¹)</strong></td>
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<tr>
<td>Low dose†</td>
<td>388 ± 32</td>
<td>360 ± 24</td>
<td>353 ± 31§</td>
<td>341 ± 26</td>
<td>374 ± 21</td>
<td>349 ± 36</td>
<td>351 ± 26‡</td>
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<tr>
<td>High dose*</td>
<td>359 ± 40</td>
<td>334 ± 31§</td>
<td>303 ± 26§</td>
<td>287 ± 42‡</td>
<td>364 ± 28</td>
<td>344 ± 49</td>
<td>345 ± 29</td>
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<td><strong>SVR (mmHg·min⁻¹·ml⁻¹)</strong></td>
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<tr>
<td>Low dose</td>
<td>0.82 ± 0.13</td>
<td>0.82 ± 0.06</td>
<td>0.87 ± 0.11</td>
<td>0.85 ± 0.07</td>
<td>0.93 ± 0.04</td>
<td>0.72 ± 0.08</td>
<td>1.04 ± 0.38</td>
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<tr>
<td>High dose*</td>
<td>0.88 ± 0.14</td>
<td>1.09 ± 0.14§</td>
<td>0.67 ± 0.08§</td>
<td>0.89 ± 0.13</td>
<td>0.98 ± 0.06</td>
<td>1.14 ± 0.10§</td>
<td>0.89 ± 0.26</td>
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</table>

Values are mean ± SD for low dose (20 mg·kg⁻¹) and high dose (45 mg·kg⁻¹). CO = cardiac output; CI = cardiac index; MAP = mean arterial pressure; HR = heart rate; SVR = systemic vascular resistance.

*P < 0.01, differences within dose group by ANOVA.
†P < 0.05, differences within dose group by ANOVA.
‡P < 0.01 versus baseline value within dose group by Dunnett’s multiple comparison test.
§P < 0.05 versus baseline value within dose group by Dunnett’s multiple comparison test.

### Table 2. Temporal Effects of Thiopental on Arterial Blood Characteristics

<table>
<thead>
<tr>
<th>Measurement Time (min)</th>
<th>Baseline</th>
<th>1</th>
<th>5</th>
<th>30</th>
<th>90</th>
<th>180</th>
<th>420</th>
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<tbody>
<tr>
<td><strong>Pao₂ (mmHg)</strong></td>
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<tr>
<td>Low dose</td>
<td>101 ± 21</td>
<td>92 ± 5</td>
<td>93 ± 31</td>
<td>94 ± 4</td>
<td>94 ± 3</td>
<td>94 ± 6</td>
<td>94 ± 4</td>
</tr>
<tr>
<td>High dose</td>
<td>467 ± 32</td>
<td>404 ± 129</td>
<td>375 ± 24</td>
<td>435 ± 110</td>
<td>390 ± 67</td>
<td>425 ± 185</td>
<td>482 ± 58</td>
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<tr>
<td><strong>Paco₂ (mmHg)</strong></td>
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<tr>
<td>Low dose†</td>
<td>35 ± 5</td>
<td>42 ± 4‡</td>
<td>40 ± 6</td>
<td>33 ± 2</td>
<td>36 ± 5</td>
<td>35 ± 3</td>
<td>38 ± 4</td>
</tr>
<tr>
<td>High dose*</td>
<td>38 ± 2</td>
<td>67 ± 10‡</td>
<td>59 ± 4§</td>
<td>53 ± 6§</td>
<td>48 ± 3‡</td>
<td>48 ± 5§</td>
<td>47 ± 7§</td>
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<tr>
<td><strong>pH</strong></td>
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<tr>
<td>Low dose†</td>
<td>7.40 ± 0.12</td>
<td>7.43 ± 0.03</td>
<td>7.36 ± 0.09</td>
<td>7.49 ± 0.02</td>
<td>7.39 ± 0.17</td>
<td>7.49 ± 0.02</td>
<td>7.46 ± 0.03</td>
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<td>High dose*</td>
<td>7.47 ± 0.03</td>
<td>7.29 ± 0.07§</td>
<td>7.29 ± 0.05§</td>
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<td>7.37 ± 0.03§</td>
<td>7.40 ± 0.03§</td>
<td>7.43 ± 0.05</td>
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<td><strong>Hct (%)</strong></td>
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<tr>
<td>Low dose</td>
<td>42 ± 13</td>
<td>22 ± 2</td>
<td>13 ± 2</td>
<td>9.4 ± 1.7</td>
<td>6.7 ± 1.4</td>
<td>3.8 ± 2.2</td>
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</tr>
<tr>
<td>High dose</td>
<td>103 ± 22</td>
<td>56 ± 5</td>
<td>34 ± 6</td>
<td>28 ± 3</td>
<td>25 ± 3</td>
<td>21 ± 3</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± SD for low dose (20 mg·kg⁻¹) and high dose (45 mg·kg⁻¹). High-dose animals received supplemental oxygen.

*P < 0.01, within dose group by ANOVA.
†P < 0.05, within dose group by ANOVA.
‡P < 0.01 versus baseline value within dose group by Dunnett’s multiple comparison test.
§P < 0.05 versus baseline value within dose group by Dunnett’s multiple comparison test.

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8 to 5 ± 1 ml·min⁻¹·100 g⁻¹, \( P < 0.05 \) and fat (25 ± 9 to 11 ± 3, \( P < 0.01 \)). Decreased blood flows were accompanied by an increase in resistance at 1 min in muscle (11 ± 6 to 19 ± 2 mmHg·ml⁻¹·min·100 g, \( P < 0.01 \)) and in fat (4.7 ± 1.3 to 9.1 ± 3.3, \( P < 0.05 \)). Blood flows to skin did not change. Testicular blood flows decreased across all time points by 25 ± 19% (\( P < 0.01 \)).

Figure 2 indicates a momentary increase in intestinal flows at 5 min after the high dose. Blood flows increased at 5 min in the small intestine (218 ± 48 to 307 ± 90 ml·min⁻¹·100 g⁻¹, \( P < 0.05 \)) and the large intestine (206 ± 50 to 273 ± 59, \( P < 0.05 \)). Concurrently, vascular resistance decreased in the small (0.47 ± 0.12 to 0.24 ± 0.07 mmHg·ml⁻¹·min·100 g, \( P < 0.01 \)) and large intestines (0.50 ± 0.10 to 0.27 ± 0.08, \( P < 0.01 \)). In the other splanchnic organs, blood flow decreased at 1 min. Pancreatic blood flow decreased for both doses during the entire experiment. Measurements of hepatic artery blood flows were highly variable with coefficients of variation ranging from 43% to 99%. Calculated liver and portal vein flows differed with time after the high dose. There appears to be momentary increases at 5 min, although no statistically significant changes were detected.

Figure 3 describes the moderate and relatively stable depressive effects of thiopental on blood flows to brain and kidney. After the high dose, brain blood flow decreased across all time points by 25 ± 19% (\( P < 0.01 \)), and resistance increased by 23 ± 31% (\( P < 0.05 \)). The percent decrease in renal blood flows for both doses together was 17 ± 15% (\( P < 0.01 \)). Heart blood flow decreased after the high dose at 1 min (389 ± 85 to 225 ± 66 ml·min⁻¹·100 g⁻¹, \( P < 0.05 \)), and resistance increased (0.28 ± 0.05 to 0.43 ± 0.13 mmHg·ml⁻¹·min·100 g, \( P < 0.05 \)). Bronchial blood flow displayed a wide range of variability with coefficient of variations ranging from 17% to 126%.

An interpretation of the cardiovascular response to the high dose of thiopental is presented in figure 4. At 1 min, cardiac output decreases and is accompanied by decreased muscle and fat blood flow, and increased systemic and peripheral resistances. Muscle and fat account for 50% of the total change in cardiac output. The momentary return to baseline in cardiac output at 5 min corresponds with increased intestinal flows, and decreased systemic and intestinal resistances. The intestines account for all of the changes in systemic resistance. By 30 min, the cardiovascular system has stabilized at a moderately depressed level, and gradually returns toward baseline conditions.

**Discussion**

This study reports thiopental-induced changes in cardiac output and regional blood flows in unrestrained chronically instrumented rats. This knowledge is necessary to understand the degree to which thiopental's
cardiovascular pharmacodynamics affects the pharmacokinetics of thiopental as well as other drugs used for induction of anesthesia. The data summarized in figure 4 describe acute decreases in muscle and fat blood flows and increases in intestinal flows supporting a previous study of pentobarbitral in rats.\textsuperscript{15} The changes in peripheral and intestinal flows and resistances correspond temporally with alterations in cardiac output and systemic vascular resistance.

In this study, the high dose of thiopental depressed cardiac output, mean arterial pressure, and heart rate.

The decreases in cardiac output and blood pressure are similar in magnitude to observations after rapid and steady-state pentobarbital administration in rats,\textsuperscript{16–18} and rapid thiopental administration in humans.\textsuperscript{19} Bradycardia usually is observed in rats,\textsuperscript{16–18} whereas humans\textsuperscript{19} and dogs\textsuperscript{20} exhibit a tachycardic response to thiopental. Because thiopental causes peripheral vasoconstriction,\textsuperscript{21} the different heart rate responses could be related to increased hemodynamic sensitivity to hypovolemia in rats.\textsuperscript{22} The comparable alterations in cardiac output and blood pressure suggests that thiopental
is changing regional blood flows in rats and humans similarly, which lends confidence to the use of the rat model for pharmacokinetic purposes.

The increased muscle resistance after the high dose of thiopental is surprising in view of the inhibitory effects of thiopental on, for example, peripheral venous tone,\textsuperscript{21} aortic and portal vein vasomotion,\textsuperscript{22} and muscle sympathetic nerve activity and the baroreceptor reflex.\textsuperscript{23} Other investigators have observed barbiturate-induced increases in muscle resistance in rats\textsuperscript{24,25} and humans.\textsuperscript{26} One possible component of the increased resistance is through autoregulation in response to decreased metabolic needs. Abdominal muscle flow decreased 33\% from active to inactive rats.\textsuperscript{27} Baroreceptor reflex compensation may play a role, because barbiturate-induced vasoconstriction in the hindquarters of rats was decreased by ganglionic blockade, and was not observed when the buffer nerves were severed.\textsuperscript{25} Direct vasoconstriction is possible. Thiopental has been shown to contract aortic smooth muscle\textsuperscript{23} and constrict resistance vessels of skeletal muscle.\textsuperscript{28}

Momentary mesenteric vasodilation has been observed previously after pentobarbital injection.\textsuperscript{15} The investigators suggested direct inhibition of smooth muscle in resistance vessels, because the vasodilation was present after either adrenalectomy or severance of the splanchnic nerves. In dogs, pentobarbital anesthesia caused an initial rise in mesenteric flow that was not significant, followed by a decline after 10 min.\textsuperscript{20} The decreased intestinal resistances in our study also could have been triggered by increased PaCO$_2$. Dogs demonstrated an increase in mesenteric blood flow when suddenly exposed to 4–8 volume percent inspired carbon

\textbf{Fig. 3.} Blood flow to highly perfused tissues after a low dose (20 mg·kg$^{-1}$) or high dose (45 mg·kg$^{-1}$) of thiopental. Values are mean ± SD. Within-group differences assessed by analysis of variance (*$P < 0.05$, **$P < 0.01$). Differences from baseline made with Dunnett's multiple comparison test (\textsuperscript{2}$P < 0.05$, **$P < 0.01$).

\textbf{Fig. 4.} The role of peripheral tissues and intestinal organs in the cardiovascular response to a high dose (45 mg·kg$^{-1}$) of thiopental. CO = cardiac output. SVR = systemic vascular resistance.
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dioxide. Other studies have reported moderate decreases in splanchnic flows during stable pentobarbital anesthesia in rats, and no change during normocapnic stable thiopental-nitrous oxide anesthesia in humans. Comparison with experiments at steady state may be inappropriate.

In our study, brain blood flow decreased 25% after the high dose of thiopental. The direction and magnitude are consistent with those reported by others. Thiopental decreases cerebral metabolic rate, which probably causes the decrease in brain blood flow. Thiopental-induced alterations in brain blood flow will affect the rate at which thiopental enters and leaves the brain, and thus the onset and offset of thiopental's hypnotic effect.

The general depression in cardiovascular activity in our study is probably not caused by hypoxia or hypocapnia. Pure oxygen has been reported not to affect cardiac output, heart rate, and blood pressure in animals anesthetized with pentobarbital, but did decrease renal blood flow to a similar extent observed on our study. Carbon dioxide increases cardiac output, blood pressure, heart rate, and blood flows in conscious humans through stimulation of the central nervous system and dilation of peripheral resistance vessels. This cardiovascular excitation is incompletely suppressed by general anesthetics. If normocarbia had been maintained in our study, then the cardiodepressive effects of thiopental may have been more severe.

We used the preanesthetic flows to investigate the effects of anesthesia. The ideal control study would measure blood flows in freely moving nonanesthetized rats for longer than 40 min, but would be difficult to perform because of the presence of the catheters and the mobility of the rats. We cannot with 100% certainty exclude all natural or experimental confounding variables. However, we have addressed the role of some of the obvious factors such as ventilatory status, and believe that the data reflect thiopental’s activity.

Interference between energy spectral peaks emitted by the different microsphere isotopes constrains the number of flow measurements per rat. With the four isotopes chosen, we frequently observed 30% spillover from the higher to lower channels. With seven isotopes, the spillover would have been greater, thus reducing counting accuracy. This necessitated splitting each thiopental dose group into two subgroups, where each subgroup was measured at baseline but at different postinjection times. Paired statistical tests were restricted to comparisons between baseline and postinjection responses to ensure that the tested groups contained common animals.

Baseline cardiac output, heart rate, and muscle blood flows in this study were less than we had reported previously in nonanesthetized rats restrained in a body sling, but similar to values reported by other investigators where stress was minimized by performing the study in a small dark box designed to mimic a burrow. Stress is thought to increase cardiac output and shift flow distribution from visceral organs to skeletal muscle. The type of restraint is an important experimental consideration influencing the hemodynamic response to a drug.

Our values for cardiac output and most regional blood flows in conscious unrestrained rats are within 55% of measurements from other studies of cardiac output distribution. Bronchial blood flows were the only exception being 85% greater than reported previously, possibly an indication of arteriovenous shunt. Reports of hepatic artery flow varies threefold in the literature. The variability in hepatic artery and bronchial flows within our study and across studies suggests that these flow measurements should be interpreted cautiously.

Our next step in this research is to combine the flows measured in this study and tissue concentrations measured in a previous study to develop a computer model of total body thiopental distribution in the rat. Previously, physiologically based pharmacokinetic models employing constant blood flows have been constructed for thiopental in humans and rats. Models describing opioid distribution have been developed in rats and scaled to humans. We will use the changing blood flows measured in this study to improve these models, and quantitate the effects of thiopental pharmacodynamics on thiopental pharmacokinetics through computer simulation.

In summary, the main effects of a thiopental bolus on regional hemodynamics in the rat are decreased blood flows and vasoconstriction in muscle and fat tissue, and a momentary vasodilatory increase in intestinal flows. Blood flows to the kidney and brain are depressed at a stable level. The changes in regional blood flows correspond to changes in cardiac output, and may play an important role in the distribution pharmacokinetics of thiopental.

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