β-Adrenergic Blockade Affects Initial Drug Distribution Due to Decreased Cardiac Output and Altered Blood Flow Distribution

Michael J. Avram, Tom C. Krejcie, Thomas K. Henthorn, and Claus U. Niemann

Department of Anesthesiology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois

Received April 16, 2004; accepted June 11, 2004

ABSTRACT

β-Adrenergic receptor blockers decrease intravenous anesthetic dose requirements. The present study determined the effect of propranolol on indocyanine green and antipyrine disposition from the moment of rapid intravenous injection. Antipyrine is a physiological marker that distributes to a volume as large as total body water in a blood flow-dependent manner and is a pharmacokinetic surrogate for many lipophilic drugs, including intravenous anesthetics. Antipyrine and indocyanine green disposition were determined twice in five healthy adult males in this Institutional Review Board-approved study, once during propranolol infusion. After rapid indocyanine green and antipyrine injection, arterial blood samples were collected frequently for 2 min and less frequently thereafter. Plasma indocyanine green and antipyrine concentrations were measured by high-performance liquid chromatography. Indocyanine green and antipyrine disposition were characterized, using SAAM II, by a recirculatory pharmacokinetic model that describes drug disposition from the moment of injection. Parameters were compared using the paired t test. The disposition of indocyanine green demonstrated that propranolol decreased cardiac output at the expense of the fast peripheral (nonsplanchnic) intravascular circuit. The area under the antipyrine concentration versus time relationship was doubled for at least the first 3 min after injection due to both decreased cardiac output and maintenance of nondistributive blood flow at the expense of a two-thirds reduction of blood flow (intercompartmental clearance) to the rapidly equilibrating (fast, splanchnic) tissue volume. The increase in antipyrine area under the curve due to propranolol-induced alteration of initial antipyrine disposition could explain decreased intravenous anesthetic dose requirements in the presence of β-adrenergic receptor blockade.

β-Adrenergic receptor blockade has been reported to decrease intravenous anesthetic dose requirements. Chronically administered propranolol decreased the sufentanil dose required to produce unconsciousness (Stanley et al., 1982). The acute administration of esmolol decreased potent volatile anesthetic requirements to prevent movement in response to the hypnotic concentration of propofol, it decreased the propofol dose requirement significantly, as reflected in the increased bias and inaccuracy of a target-controlled infusion (Orme et al., 2002). Although the mechanism by which β-blockers decrease intravenous anesthetic dose requirements is unclear, the latter observation suggests that the interaction is pharmacokinetic (Orme et al., 2002). Pharmacokinetic interactions with β-blockers are not unexpected because they decrease cardiac output and hepatic blood flow, so they would be expected to decrease the elimination clearance of high clearance drugs (Conrad et al., 1983). However, altered elimination clearance is unlikely to affect dose requirements of acutely administered, rapidly acting intravenous agents (Krejcie and Avram, 1999).

Interindividual variability in response to intravenous anesthetics is well known but poorly understood (Dundee et al., 1982; Christensen and Andreasen, 1990). Price (1960) recognized the importance of cardiac output on early drug concentrations after rapid intravenous administration reasoning, for example, that the hypnotic dose requirement of patients in hemorrhagic shock is less because the fraction of the dose received by their brain is high and its rate of removal is low due to decreased blood flow to indifferent tissues. However, a study of the patient-specific variables age, sex, weight, lean body mass, and cardiac output that were associated with differences in thiopental induction dose requirements revealed that cardiac output alone could not account for inter-
individual differences in dose requirements (Avram et al., 1993). We therefore developed a recirculatory pharmacokinetic model to describe the effect of both cardiac output and peripheral blood flow distribution on early drug concentration history after rapid intravenous administration (Krejcie et al., 1996a). Using this model in mildly and moderately hypovolemic dogs, we were able to demonstrate that the increase in the area under the drug concentration versus time relationship (area under the curve; AUC) in the critical first minutes after rapid intravenous drug administration was due to not only decreased cardiac output but also to an increase in the fraction of cardiac output that was nondistributive (Krejcie et al., 1999), that is, that returned drug to the central circulation after minimal apparent tissue distribution (Krejcie et al., 1996a).

The recirculatory pharmacokinetic model has been used to describe the concomitant disposition of markers with well defined distribution, including indocyanine green (ICG) and antipyrine, from the moment of rapid intravenous injection based on frequent early arterial blood sampling. Indocyanine green is an intravascular marker because it binds to plasma proteins rapidly and completely, impeding its extravascular distribution (Baker, 1966). Combined description of both the monoexponential blood indocyanine green concentration history and its first-pass and subsequent recirculation peaks (the mixing phase) using a recirculatory pharmacokinetic model (Fig. 1) allows characterization of intravascular events, such as mixing, by deriving estimates of not only blood volume and cardiac output but also their systemic distribution (Henthorn et al., 1992; Krejcie et al., 1996a; Niemann et al., 2000). Antipyrine is a marker of total body water (Soberman et al., 1949), including pulmonary extravascular water (Brigham et al., 1971), and it distributes to a volume as large as total body water in a blood flow-dependent manner (Renkin, 1952, 1955). Antipyrine is, therefore, a pharmacokinetic surrogate for many lipophilic drugs, including intravenous anesthetics (Avram et al., 2002), and a recirculatory model of its disposition (Fig. 1) can be used to describe the role of cardiac output and peripheral blood flow distribution in the disposition of lipophilic drugs while meeting the assumption of system stationarity.

The present study is an extension of our previous study of the effect of propranolol on human blood volume and blood flow distribution (Niemann et al., 2000). It was designed to test the hypothesis that β-adrenergic receptor blockade will increase antipyrine area under the curve in the critical first minutes after rapid intravenous administration as a result of both decreased cardiac output and an increased fraction of cardiac output represented by nondistributive blood flow.

Materials and Methods

Experimental Protocol. The study was conducted as described previously (Niemann et al., 2000). Five healthy, fit, fasting adult male volunteers were studied on two occasions each, the order of which was randomly determined, after obtaining institutionally approved, written, informed consent. After an overnight fast, they were admitted to the General Clinical Research Center of Northwestern University’s Feinberg School of Medicine. Volunteers were supine from at least 2 h before drug administration until at least 1 h thereafter. The radial artery at the wrist of the nondominant arm was cannulated percutaneously with a 20-g, 2-in-long catheter, whereas a 16-g, 2-in-long catheter was placed in the cephalic vein of the ipsilateral upper arm. Blood samples were obtained through the arterial catheter, whereas the venous catheter was used for drug and fluid administration.

When the effect of propranolol was to be studied, propranolol was administered by a computer-controlled intravenous infusion (Stanpump, Stanford University, Stanford, CA; Stanpump software, implemented on a notebook personal computer, drove a Harvard Pump 22 syringe pump (Harvard Apparatus Inc., Holliston, MA) demonstrated to produce pseudo steady-state plasma propranolol concentrations of 30 ng/ml for the duration of the study (Niemann et al., 2000). This concentration represents average trough plasma propranolol concentrations during steady-state administration of 60-mg oral doses three times per day to healthy young males and produces at least a 20 beat per minute reduction of exercise-induced tachycardia (Coelho et al., 1983). The study was not begun until the propranolol infusion had run for at least 20 min to ensure equilibration of effector sites with plasma.

Five to seven hundred milliliters of a 0.9% sodium chloride solution was infused intravenously before beginning the study. After a short period of stabilization, blank blood was withdrawn for construction of the indocyanine green standard curve. The study was not begun until the subject was determined to be hemodynamically stable.

![Fig. 1. General model for the recirculatory pharmacokinetics of ICG and antipyrine (Krejcie et al., 1996a). Cardiac output (CO) flows through the central circulation, which is defined by the parallel delay elements (V_C). All delay elements are represented generically by rectangles surrounding four compartments, although the number of compartments needed in a delay varied between 2 and 30. The pulmonary tissue volume (V_{T,P}), a subset of V_C, is calculated for antipyrine by subtracting the V_C of indocyanine green from that of antipyrine. Beyond the central circulation, cardiac output distributes to numerous circulatory and tissue circuits that lump, on the basis of their blood volume to flow ratios or tissue volume to distribution clearance ratios (mean transit times), into fast (V_{ND,F}, CL_{ND,F}) and slow (V_{ND,S}, CL_{ND,S}) peripheral blood circuits (indocyanine green) or the nondistributive peripheral circuit (V_{ND}, CL_{ND}) and the fast (V_{T,F}, CL_{T,F}) and slow (V_{T,S}, CL_{T,S}) tissue volume groups (antipyrine). Indocyanine green, which distributes only within the intravascular space, does not have fast and slow tissue volumes. The nondistributive flow for indocyanine green was resolved into fast and slow components; antipyrine does not have an identifiable (i.e., mathematically distinct) second nondistributive peripheral circuit. The elimination clearances (CL_P) are modeled from the arterial sampling site without being associated with any particular peripheral circuit.](image-url)
Indocyanine green (IC-Green; Akorn, Inc., Buffalo Grove, IL) (10 mg in 2 ml of diluent) and antipyrine (Parenteral Medications Laboratory, Department of Pharmaceutics, University of Tennessee, Memphis, TN) (50 mg in 1 ml) were placed sequentially in a 150-cm length of intravenous tubing and connected to the cephalic vein catheter via a stopcock. At the onset of the study (time \( t = -0.05 \) min), the drug volume was flushed into the stream of the rapidly running intravenous infusion within 5 s using 10 ml of saline. Arterial blood samples were collected every 0.03 min for the first 0.48 min and every 0.06 min for the next 0.54 min using a computer-controlled roller pump (Masterflex; Cole-Parmer Instrument Co., Chicago, IL), set at a withdrawal rate of 1 ml/s, and a chromatography fraction collector (model 203; Gilson Medical Electronics, Middleton, WI). Subsequent arterial blood samples were drawn manually at 0.2-min intervals to 2 min, at 0.5-min intervals to 4 min, at 1-min intervals to 6 min, and at less frequent intervals to 360 min.

**Physiological Measurements.** Systemic blood pressure and heart rate were determined by an oscillometric technique (Datascope Accumet, Paramus, NJ). Arterial oxygen saturation and heart rate were monitored continuously by a pulse oximeter (Datascope Accusat). Systemic vascular resistance was calculated retrospectively from the dye (indocyanine green) dilution cardiac output and mean arterial pressure.

**Analytical Methods.** Plasma indocyanine green concentrations of all samples obtained up to 20 min were measured on the study day using high-performance liquid chromatography (Henthorn et al., 1992). Plasma antipyrine concentrations were measured in all samples using a high-performance liquid chromatography technique developed in our laboratory (Krejcie et al., 1994, 1996a). To interpret intercompartmental clearances in relation to blood flow, the recirculatory models were constructed on the basis of whole blood marker concentrations. Plasma indocyanine green concentrations were converted to blood concentrations by multiplying them by 1 - the hematocrit, because indocyanine green does not partition into erythrocytes (Rowland, 1972). Plasma antipyrine concentrations were converted to blood concentrations using an in vivo technique that corrects for antipyrine partitioning into erythrocytes by calculating its apparent dose assuming a red blood cell/plasma partition coefficient of 1 (Krejcie et al., 1996a,b).

**Pharmacokinetic Model.** The pharmacokinetic modeling method (Fig. 1) has been described in detail previously (Krejcie et al., 1996a; Avram et al., 1997). The sum of two Erlang distribution functions were developed in our laboratory (Krejcie et al., 1994, 1996a). The eight model variables determined from indocyanine green concentrations and the 10 independent model variables determined from antipyrine concentrations have been determined to be both sensible and identifiable for our sampling schedule by the IDENT2 program (Jacquez and Perry, 1990; Krejcie et al., 1996a).

The area under the arterial blood antipyrine concentration versus time relationships were determined for each of the first 3 min after rapid intravenous administration of 50 mg during both the control and propranolol studies. As discussed below, an increased area under the antipyrine concentration versus time curve was observed in the propranolol studies. This could have one of two causes. Propranolol could increase the area under the curve either as a result of a decrease in cardiac output alone or as a result of both a decrease in cardiac output and an increase in the fraction of cardiac output represented by non-distributive blood flow. To help distinguish between these options, we performed simulations of the antipyrine concentration versus time relationship for each subject using SAAM II. In performing the simulations, we made the common assumptions of physiological pharmacokinetic modeling: regional blood flows (clearances) to unaltered tissue volumes are adjusted in direct proportion to measured changes in cardiac output (Davis and Mapleb, 1993). The central circulation for each subject, including cardiac output, was that determined in their respective propranolol study. The volumes \( V_{SD}, V_{SP}, V_{ST} \), and \( V_{SDT} \) were fixed to those determined in their control study, whereas the clearances \( CL_{S-D}, CL_{S-P}, \) and \( CL_{S-T} \) were fixed to the respective control clearances reduced in proportion to the lower cardiac output observed in the propranolol study (i.e.,

### Table 1

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Age</th>
<th>Weight</th>
<th>Heart Rate</th>
<th>Mean Arterial Pressure</th>
<th>Cardiac Output</th>
<th>Systemic Vascular Resistance</th>
<th>Indocyanine Green</th>
<th>Antipyrine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>yr</td>
<td>kg</td>
<td>BPM</td>
<td>mm Hg</td>
<td>l/min</td>
<td>dyn · s · cm⁻⁵</td>
<td>VₜS</td>
<td>CLₜS</td>
</tr>
<tr>
<td>Control</td>
<td>35 ± 9</td>
<td>80 ± 15</td>
<td>53 ± 11</td>
<td>94 ± 11</td>
<td>9.8 ± 0.7</td>
<td>796 ± 163</td>
<td>72 ± 11</td>
<td>605 ± 156</td>
</tr>
<tr>
<td>Propranolol</td>
<td>35 ± 9</td>
<td>80 ± 15</td>
<td>49 ± 7</td>
<td>97 ± 8</td>
<td>4.3 ± 0.9*</td>
<td>1853 ± 491*</td>
<td>64 ± 7</td>
<td>587 ± 35</td>
</tr>
</tbody>
</table>

BPM, beats per minute.  
* Determined by dye (indocyanine green) dilution at the moment of marker injection.  
* Mean central venous pressure assumed to be zero.  
* Significantly different from control, \( p < 0.05 \).
equilibrating nondistributive (ND-F) and slowly equilibrating (slow) nondistributive (ND-S) intravascular circuits, elimination clearance (CLE), and the sum of all clearances were determined for each of the first 3 min of the simulations. These clearances were compared using the paired t test. More than two observations were compared using the repeated measure analysis of variance, with all possible post hoc comparisons carried out using Fisher’s least significant difference test. The criterion for rejection of the null hypothesis was \( p < 0.05 \).

**Results**

Propranolol treatment had no effect on either heart rate or mean arterial pressure in our physically fit volunteers but resulted in a significant decrease in cardiac output and an increase in calculated systemic vascular resistance (Table 1). Both the blood indocyanine green and blood antipyrine concentration versus time relationships were well characterized by the model from the moment of injection (Figs. 2 and 3). The one-sample runs test confirmed that there were no systematic deviations of the observed data from the calculated values. Visual comparison of the measured and predicted marker concentration versus time relationships revealed no model misspecification.

**Indocyanine Green Pharmacokinetics.** Both the cardiac output determined by indocyanine green and indocyanine green CLE were decreased significantly by propranolol (Table 1), on average, cardiac output decreased by 56% and indocyanine green CLE decreased by 24%. There was also a significant decrease in the intercompartamental clearance of the fast nondistributive circuit (CLND-F) (Table 2). CLND-F represented 60% of cardiac output in the volunteers in the absence of propranolol and decreased to 33% of the diminished cardiac output in the same subjects during the propranolol infusion, thus accounting for over 80% of the decrease in cardiac output. The actual value of the intercompartamental clearance of the slow nondistributive circuit (CLND-S) was unchanged in the volunteers during the propranolol infusion (Table 2) and therefore represented a larger percentage (27% in control studies versus 45% in propranolol studies) of the diminished cardiac output.

Although the total volume of distribution \( V_{SS} \) of indocyanine green was not affected by propranolol (Tables 1 and 2), blood volume distribution within the peripheral intravascular circuits was significantly affected by propranolol (Table 2).

**Table 2** Pharmacokinetic variables for the recirculatory indocyanine green pharmacokinetic model \( n = 5 \)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>V&lt;sub&gt;C&lt;/sub&gt; (l)</th>
<th>V&lt;sub&gt;ND-F&lt;/sub&gt; (l)</th>
<th>V&lt;sub&gt;ND-S&lt;/sub&gt; (l)</th>
<th>V&lt;sub&gt;BS&lt;/sub&gt; (l)</th>
<th>CL&lt;sub&gt;ND-F&lt;/sub&gt; (l/min)</th>
<th>CL&lt;sub&gt;ND-S&lt;/sub&gt; (l/min)</th>
<th>CL&lt;sub&gt;E&lt;/sub&gt; (l/min)</th>
<th>ΣCL (l/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1.45 ± 0.37</td>
<td>1.42 ± 0.74</td>
<td>2.96 ± 1.64</td>
<td>5.83 ± 1.51</td>
<td>5.89 ± 3.52</td>
<td>2.69 ± 1.41</td>
<td>1.25 ± 0.17</td>
<td>9.83 ± 2.68</td>
</tr>
<tr>
<td>Propranolol</td>
<td>1.04 ± 0.23*</td>
<td>0.48 ± 0.15*</td>
<td>3.55 ± 0.47</td>
<td>5.07 ± 0.65</td>
<td>1.45 ± 0.19*</td>
<td>1.95 ± 0.51</td>
<td>0.95 ± 0.33*</td>
<td>4.35 ± 0.85*</td>
</tr>
</tbody>
</table>

*Significantly different from control, \( p < 0.05 \).
The blood volume in the fast nondistributive circuit (V_{ND,F}) decreased significantly from 24 to 10% of the total blood volume as a result of the effect of propranolol. Although the change in blood volume in the slow nondistributive circuit (V_{ND,S}) did not reach statistical significance during the propranolol infusion, it did increase from 51 to 70% of the total blood volume (Fig. 1; Table 2).

**Antipyrine Pharmacokinetics.** The propranolol infusion affected antipyrine disposition mainly through changes in the intercompartmental clearances and the fraction of cardiac output they represent (Table 3; Fig. 4). As cardiac output decreased on average by 56% during the propranolol infusion, CLND and CLT-S remained virtually unchanged but CLT-F decreased by nearly 70% compared with control values. As a result of the propranolol-induced cardiovascular changes, the fraction of cardiac output represented by both CLND and CLT-S nearly doubled from 12% of the control cardiac output each to 24 and 21% of the cardiac output during the propranolol infusion, respectively (Fig. 4). The fraction of cardiac output represented by CLT-F decreased from 76% under control conditions to 54% during the propranolol infusion (Fig. 4).

The antipyrine distribution volume most affected by the propranolol was V_{T-F}, which decreased by approximately 50% during the propranolol infusion (Table 3; Fig. 4). During the propranolol infusion, V_{T-S} increased in size by a volume nearly equal to that by which V_{T-F} decreased, although this increase was not statistically significant (Table 3). As a result of these changes, V_{T-F} represented approximately 43% of peripheral tissue distribution volume (V_{T-F} + V_{T-S}) under control conditions but decreased during the propranolol infusions to represent approximately 23% of peripheral tissue distribution volume (Fig. 4). The pulmonary tissue volume, V_{T-P} (Brigham et al., 1971), and the single peripheral nondistributive volume that could be independently resolved in the antipyrine model, V_{ND} (Krejcie et al., 1996a), were not changed significantly as a result of the propranolol infusion.

**TABLE 3**

Pharmacokinetic variables for the recirculatory antipyrine pharmacokinetic model (n = 5)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>V_C</th>
<th>V_{T-F}</th>
<th>V_{ND}</th>
<th>V_{T-F}</th>
<th>V_{T-S}</th>
<th>V_{SS}</th>
<th>CL_{ND}</th>
<th>CL_{T-F}</th>
<th>CL_{T-S}</th>
<th>CL_E</th>
<th>ΣCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>2.67</td>
<td>20.25</td>
<td>0.28</td>
<td>26.76</td>
<td>6.45</td>
<td>49.75</td>
<td>0.93</td>
<td>1.45</td>
<td>1.14</td>
<td>0.66</td>
<td>9.83</td>
</tr>
<tr>
<td>Propranolol</td>
<td>1.02</td>
<td>10.29</td>
<td>0.15</td>
<td>34.20</td>
<td>5.32</td>
<td>46.78</td>
<td>0.68</td>
<td>0.30</td>
<td>0.20</td>
<td>0.05</td>
<td>4.35</td>
</tr>
</tbody>
</table>

*Significantly different from control, *p* < 0.05.

**Fig. 4.** The upper two pie charts illustrate the volumes (V) of the central circuit (C), nondistributive (ND) circuit, and the rapidly equilibrating (fast) (T-F) and slowly equilibrating (slow) (T-S) tissues as percentage of the total volume of distribution (V_{SS}), comparing control values (left) to those determined during the pseudo steady-state propranolol infusion (right). The lower two pie charts illustrate the clearances (CL) of the nondistributive (ND) circuit, the rapidly equilibrating (fast) (T-F) and slowly equilibrating (T-S) tissues, and elimination clearance (E) as percentage of total clearance (ΣCL, cardiac output), comparing control values (left) to those determined during the pseudo steady-state propranolol infusion (right).
whereas the lines represent concentrations predicted by the models. The symbols represent antipyrine concentrations, regional blood flows change in direct proportion to the change in cardiac distribution volumes are unchanged from control by propranolol, whereas closed symbols) and a simulation based on the assumption that regional injection in 1 of the 5 subjects during the propranolol infusion (dark line, Fig. 5.

### Areas Under the Blood Concentration versus Time Relationships

Propranolol nearly doubled the antipyrine area under the curve in the first 3 min after rapid intravenous administration compared with the control areas under the curves in the same individuals (Table 4). Propranolol similarly increased not only the area under the curve of the first minute after drug administration, which includes the first-pass peak determined by cardiac output, but also those of each of the next 2 min, which approximately represent recirculation and early drug distribution, respectively (Fig. 3).

The areas under the curves of the first 3 min of the simulated antipyrine concentration histories were also larger than those of the controls, but because of unchanged peripheral flow distribution, this increase was almost entirely a result of the increased first-pass areas under the curves during the first minute after drug administration (Figs. 3 and 5; Table 4). Because the areas under the curves of the simulated second and third minute increased minimally, the cumulative areas under the curves for the first 3 min of the simulated antipyrine concentration histories were less than those actually observed during the propranolol infusion (Table 4).

### Discussion

An important observation of our previous work with various paradigms of perturbed canine physiology is that not only cardiac output but also its distribution affect early drug concentrations, as reflected in the area under the curve in the first minutes after rapid intravenous administration (Avram et al., 1997, 2000; Krecjie et al., 1999, 2001). Because of arteriovenous anastomoses or significant diffusion barriers, a fraction of cardiac output returns blood to the central circulation after minimal drug loss due to tissue distribution (Krecjie et al., 1996a; Avram et al., 1997). The recirculatory model uses the blood drug concentrations of the recirculation peak to describe this nondistributive blood flow, or nondistributive clearance, which can be thought of as a pharmacokinetic shunt. Because nondistributive blood flow quickly returns the lipophilic marker to the central circulation, an increase in the fraction of cardiac output represented by nondistributive blood flow increases the area under the initial arterial blood drug concentration versus time curve. It is during the early minutes after drug administration when drugs with a rapid onset of effect exert their maximum effect. Increased arterial drug concentrations resulting from a larger fractional $CL_{ND}$ increase drug exposure of the sites of action of these drugs, for which antipyrine is a pharmacokinetic surrogate (Renkin, 1952, 1955; Avram et al., 2002) and would be expected to produce a more profound and prolonged effect.

The cardiovascular effects of propranolol in our volunteers (Table 1) were consistent with its expected effects. Propranolol is a nonselective $\beta$-adrenergic receptor antagonist. When administered to anxious volunteers, propranolol results in increased systemic vascular resistance due to $\beta$-adrenergic receptor blockade and unopposed reflex $\alpha$-adrenergic activation and a decrease in cardiac output (Freyschuss et al., 1988; Hoffman, 2001). Given the existence of unopposed reflex $\alpha$-adrenergic activation in anxious volunteers to whom a $\beta$-adrenergic receptor blocker has been administered (Freyschuss et al., 1988; Hoffman, 2001), it could be expected that the results of the present study in humans should be similar to those of the study of the effects of the $\alpha_1$-adrenergic agonist phenylephrine in awake dogs (Krecjie et al., 2001). Indeed, both phenylephrine in awake dogs (Krecjie et al., 2001) and propranolol in awake human volunteers (Table 3) decreased cardiac output substantially (by 42% in dogs and by 56% in humans) yet had no effect on nondistributive blood flow. Thus, both phenylephrine and propranolol nearly doubled the fraction of cardiac output represented by $CL_{ND}$ at the expense of the fraction of the reduced cardiac output represented by $CL_{T,F}$ to a smaller $V_{T,F}$ (Fig. 4).

Antipyrine $V_{T,F}$ represents splanchnic tissues, whereas $V_{T,S}$ represents nonsplanchnic tissues (primarily muscle) (Sedek et al., 1989; Krecjie et al., 1996a). The ability of our

### TABLE 4

Areas under the blood antipyrine concentration versus time relationships for the first 3 min after rapid intravenous administration of 50 mg to human volunteers ($n = 5$).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC$_{0-1}$ min</th>
<th>AUC$_{1-2}$ min</th>
<th>AUC$_{2-3}$ min</th>
<th>AUC$_{0-3}$ min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>6.60 ± 1.58</td>
<td>1.91 ± 0.71</td>
<td>1.75 ± 0.72</td>
<td>10.35 ± 2.68</td>
</tr>
<tr>
<td>Propranolol</td>
<td>12.52 ± 2.07*</td>
<td>4.43 ± 2.38**</td>
<td>2.64 ± 1.04**</td>
<td>19.59 ± 5.45**</td>
</tr>
<tr>
<td>Simulation</td>
<td>12.16 ± 2.19*</td>
<td>2.40 ± 0.77</td>
<td>2.04 ± 0.76**</td>
<td>16.59 ± 3.49**</td>
</tr>
</tbody>
</table>

*Significantly different from control, $p < 0.05$.

**Significantly different from all others, $p < 0.05$.

![Fig. 5. Arterial blood antipyrine concentration history for the first 3 min (illustrating the first- and second-pass peaks) after rapid intravenous injection in 1 of the 5 subjects during the propranolol infusion (dark line, closed symbols) and a simulation based on the assumption that regional distribution volumes are unchanged from control by propranolol, whereas regional blood flows change in direct proportion to the change in cardiac output (light line). The symbols represent antipyrine concentrations, whereas the lines represent concentrations predicted by the models.](image-url)
model to describe changes in physiological marker disposition due to altered cardiac output and peripheral blood flow distribution can be evaluated by comparing blood flow-dependent antipyrene disposition during a given experimental condition to blood flow measurements made with radioactive microspheres under similar conditions. The studies most suitable for comparison are those conducted with 8- to 10- or 15-μm microspheres, which distribute like erythrocytes (but with capillary trapping) (Heymann et al., 1977). A study of organ blood flow distribution using 15-μm microspheres in awake dogs found that propranolol decreased blood flow only to splanchic organs (Dumont et al., 1984). Propranolol reduced the blood flow to splanchic organs in dogs by approximately 50% as a result of α-adrenergic-mediated vasoconstriction, an observation with which the present results in humans are consistent (Table 3). Also consistent with these data is the use of a nonselective β-blocker, such as propranolol, to decrease the hepatic venous pressure gradient and reduce the risk of recurrent variceal bleeding in patients with liver disease (Andreu et al., 2002).

During a propranolol infusion, the antipyrene areas under the curves nearly doubled during the first 3 min after rapid intravenous administration compared with the control areas under the curves in the same individuals (Table 4). This initial effect is the same as giving twice the dose of a rapidly acting lipophilic drug, for which antipyrene is a pharmacokinetic surrogate (Renkin, 1952, 1955; Avram et al., 2002) to an individual who is not β-blocked. The present results, therefore, suggest that altered initial distribution kinetics (Krejcie and Avram, 1999) is a mechanism by which β-blockers decrease intravenous anesthetic dose requirements (Stanley et al., 1982; Johansen et al., 1998; Orme et al., 2002). Indeed, Upton et al. (1999) found that in awake sheep an infusion of metaraminol, a sympathomimetic vasoconstrictor like phenylephrine, decreased cardiac output by nearly 30% and increased the area under the propofol concentration versus time relationship during and for 8 min after a 2-min propofol infusion by 43% compared with awake controls.

We conducted simulations to determine the relative contribution of decreased cardiac output and increased fraction of cardiac output represented by nondistributive blood flow to the increase in antipyrene area under the curve produced by propranolol in humans. When simulating drug disposition in the presence of altered physiology, physiological modelers adjust regional blood flows to unadjusted tissue volumes in direct proportion to changes in cardiac output (Davis and Mapleson, 1993), arbitrarily and independently (Price, 1960), or on the basis of radioactive microsphere regional blood flow measurements (Benowitz et al., 1977). In performing the present simulations, the areas under the curves observed during the first 3 min after antipyrene administration to β-blocked volunteers were compared with those predicted by the simulations making the common assumption of physiological models (Davis and Mapleson, 1993). The model architecture is based on the assumptions that regional distribution volumes are unchanged in the presence of altered physiology, whereas regional blood flow changes in direct proportion to changes in cardiac output. As expected, the observed and simulated areas under the curves did not differ during the first minute after drug administration, when the concentration versus time relationships were determined primarily by cardiac outputs (i.e., during what is primarily the first-pass area under the concentration versus time relationship) (Table 4, Fig. 5). However, the observed and simulated areas under the curves did differ significantly during the second and third minute when nondistributive blood flows and early distribution kinetics determined the concentration versus time relationship (Table 4; Fig. 5). The simulations conducted in the present study therefore confirmed that both the decreased cardiac output and increased nondistributive blood flow contributed to the increase in antipyrene area under the curve in the critical first minutes after drug administration. (Krejcie et al., 1999, 2001).

We used a pharmacokinetic model to characterize the blood indocyanine green and antipyrene concentration versus time relationships from the moment of rapid intravenous injection in human volunteers. The model incorporates data from both the initial transient oscillations and the later, postmixing portions of the curves, to provide estimates of not only blood volume and cardiac output but also their distribution among central and peripheral circuits. In the present study, this model was used to describe intravascular events and blood flow-dependent drug distribution in the presence and absence of a propranolol infusion. The disposition of concomitantly administered indocyanine green demonstrated that propranolol decreased cardiac output at the expense of the fast peripheral intravascular circuit. The area under the antipyrene concentration versus time relationship was doubled for at least the first 3 min after rapid intravenous injection due to both decreased cardiac output and minimally altered nondistributive blood flow at the expense of a twothirds reduction of blood flow (intercompartmental clearance) to the rapidly equilibrating (fast, splanchnic) tissue volume. The increase in the area under the antipyrene curve due to the propranolol-induced alteration of initial antipyrene disposition could explain decreased intravenous anesthetic dose requirements in the presence of β-adrenergic blockade. Because perioperative β-adrenergic receptor blockade to reduce cardiac morbidity and mortality in at-risk patients is becoming the standard of care, (London et al., 2004), these observations have important clinical implications.

References