Role of propofol and its solvent, intralipid, in nitric oxide-induced peripheral vasodilatation in dogs

M.-F. Doursout¹, P. M. Joseph¹, Y. Y. Liang¹, C. J. Hartley² and J. E. Chelly¹*

¹Department of Anesthesiology, The University of Texas–Houston Medical School, 6431 Fannin, MSB 5.020 Houston, TX 77030-1503, USA. ²Department of Internal Medicine, Baylor College of Medicine, Houston, Texas, USA

*Corresponding author

Background. The commercial propofol preparation in an intralipid solution causes marked vasodilatation. Both propofol and its solvent seem to stimulate the nitric oxide (NO) pathway. The role of intralipid in cardiac and regional haemodynamic changes induced by propofol and their respective interactions with the NO pathway was assessed.

Methods. Dogs were instrumented to record arterial pressure, heart rate, cardiac output, dP/dt (the first derivative of left ventricular pressure) and vertebral, carotid, coronary, mesenteric, hepatic, portal and renal blood flows. Experimental groups were as follows. Group I (control; n=11): N-methyl-L-arginine (L-NMA) 20 mg kg⁻¹ i.v.; Group 2 (n=8): propofol (10 mg ml⁻¹) 4 mg kg⁻¹ i.v. bolus followed by 0.6 mg kg⁻¹ min⁻¹; Group 3 (n=6): intralipid 0.25 ml kg⁻¹ bolus followed by 0.06 ml kg⁻¹ min⁻¹. After 60 min, L-NMA was injected in Groups 2 and 3.

Results. Propofol induced increases in heart rate, coronary and carotid blood flows, and decreases in systemic vascular resistance and dP/dt. Intralipid increased renal blood flow, carotid vascular resistance and mesenteric vascular resistance. In the presence of intralipid, L-NMA-induced pressor response and systemic, carotid and renal vasoconstriction were more pronounced than in control dogs.

Conclusions. Except for the coronary and carotid circulations, intralipid modulates the NO pathway in cardiac and regional blood flow.

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It is well established that intravenous injection of propofol produces hypotension and peripheral vasodilatation. The mechanism of its cardiovascular effects appears to be complex and is only partially understood even after more than 15 years of research. Pagel and colleagues demonstrated that propofol produces a direct negative inotropic effect that contributes to its cardiovascular properties. Lowe and colleagues demonstrated that the effects of propofol on cardiac function are also indirect and are mediated in part by an increase in aortic compliance and a decrease in systemic vascular resistance. Several mechanisms have been proposed to account for the vasodilator properties of propofol, such as inhibition of the sympathetic vasoconstrictor nerve activity, blockade of calcium channels, activation of K⁺ ATP channels and stimulation of nitric oxide (NO) production.

Propofol, which is mostly lipid soluble, is available in an intralipid solution. Although Hageman and colleagues reported that intralipid itself produced pulmonary vasodilatation, the cardiac and regional haemodynamic properties of intralipid remained unknown in vivo studies. Furthermore, studies performed in vitro demonstrated that lipid solutions also modulate endothelial NO activity and/or endothelium-dependent relaxation. Therefore, we postulated that the propofol solvent, intralipid, may also contribute to the cardiac and regional haemodynamic properties of propofol solution as well as to the propofol-mediated stimulation of the NO pathway.
Materials and methods

The University of Texas Animal Welfare Committee approved this protocol.

Cardiovascular instrumentation

A description of the basic model has been published previously.13 Briefly, mongrel dogs of either sex, heartworm free, weighing 25–34 kg, were instrumented with catheters in the iliac artery, left atrium and pulmonary artery. A precalibrated ultrasonic flow probe was positioned around the pulmonary artery and a miniature pressure transducer was inserted into the left ventricle. Pulsed Doppler flow probes were positioned around the vertebral, carotid, coronary, mesenteric, hepatic and renal arteries and the portal vein. All transducer leads and catheters were tunneled subcutaneously to the dorsum of the neck and secured after the thoracotomy was closed. Analgesia and antibiotic prophylaxis were initiated before surgery and maintained thereafter.

Measurements

A detailed description of the measurement techniques has also been published previously.13–15 Phasic and mean arterial pressure (MAP), pulmonary arterial pressure (PAP), first derivative of left ventricular pressure (dP/dt), heart rate (HR), cardiac output (CO), and carotid, vertebral, coronary, mesenteric, hepatic, portal and renal blood flow (BF) were recorded continuously on a 16-channel Gould brush polygraph. Systemic vascular resistance (SVR) and pulmonary vascular resistance (VR) were calculated as the ratio of MAP or PAP to CO; regional VR was calculated as the ratio of MAP to regional BF.

Experimental design

Dogs were carefully nursed through the first 24 h after surgery, and on subsequent days were trained to lie quietly on the laboratory floor. The dogs were studied no less than 10 days after surgery, when haematocrit was >30% and body temperature, appetite and general appearance were normal. Body weight, body temperature, arterial blood gases and haematocrit were measured before each experiment. All experiments were conducted in fasted conscious dogs lying on their right sides.

Since propofol is mostly lipid soluble, we studied the cardiac and regional haemodynamic properties of propofol and its solvent, intralipid, infused under the same experimental conditions. Furthermore, to determine the role played by intralipid in the propofol-mediated stimulation of NO, we also studied the effects of N-methyl-L-arginine (L-NMA), a non-specific inhibitor of NO synthase (NOS), on the cardiac and regional changes produced by propofol and intralipid. Accordingly, animals were randomly distributed into three groups. Animals in Group 1 (n=11, control group) received L-NMA 20 mg kg⁻¹ i.v. through a filter (Nalgene™) over 1 min. This dose was chosen because it produced maximum haemodynamic changes in conscious dogs.16 Animals in Group 2 (n=8) received propofol (10 mg ml⁻¹) 4 mg kg⁻¹ i.v. bolus followed by 0.6 mg kg⁻¹ min⁻¹ for 180 min. Animals in Group 3 (n=6) received intralipid 0.25 ml kg⁻¹ bolus followed by 0.06 ml kg⁻¹ min⁻¹ for 180 min. After 60 min, animals in Groups 2 and 3 received L-NMA 20 mg kg⁻¹ i.v. over 1 min. A mixture of nitrogen and oxygen was used to maintain arterial oxygen tension at approximately the same level as in control dogs. Blood gases were monitored every 30 min. Haemodynamic parameters were recorded before and during propofol and intralipid infusions and for 2 h after L-NMA administration.

### Table 1 Haemodynamic effects of propofol (n=8) and its solvent intralipid (n=6) recorded at baseline and 60 min before L-NMA infusion on haemodynamic parameters. dP/dt, the first derivative of left ventricular pressure. Data are mean (SEM). BF=blood flow; VR=vascular resistance. *P<0.05 vs baseline

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Group</th>
<th>Baseline</th>
<th>60 min</th>
<th>Propofol</th>
<th>Intralipid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>Intralipid</td>
<td>100 (5)</td>
<td>105 (7)</td>
<td>95 (6)</td>
<td>88 (8)</td>
</tr>
<tr>
<td>Heart rate (beats min⁻¹)</td>
<td>Intralipid</td>
<td>86 (4)</td>
<td>90 (5)</td>
<td>89 (4)</td>
<td>121 (7)*</td>
</tr>
<tr>
<td>Cardiac output (litres min⁻¹)</td>
<td>Intralipid</td>
<td>2.3 (0.50)</td>
<td>2.1 (0.4)</td>
<td>1.75 (0.2)</td>
<td>1.8 (0.2)</td>
</tr>
<tr>
<td>dP/dt (mm Hg s⁻¹)</td>
<td>Intralipid</td>
<td>3163 (196)</td>
<td>3334 (232)</td>
<td>3174 (268)</td>
<td>2622 (272)*</td>
</tr>
<tr>
<td>Systemic VR (dyne s⁻¹ cm⁻⁵)</td>
<td>Intralipid</td>
<td>56 (7)</td>
<td>57 (7)</td>
<td>64 (7)</td>
<td>51 (4)*</td>
</tr>
<tr>
<td>Carotid BF (ml min⁻¹)</td>
<td>Intralipid</td>
<td>115 (10)</td>
<td>104 (10)</td>
<td>137 (22)</td>
<td>167 (26)*</td>
</tr>
<tr>
<td>Carotid VR (dyne s⁻¹ cm⁻⁵)</td>
<td>Intralipid</td>
<td>0.96 (0.16)</td>
<td>1.12 (0.15)*</td>
<td>0.73 (0.10)</td>
<td>0.61 (0.08)</td>
</tr>
<tr>
<td>Coronary BF (ml min⁻¹)</td>
<td>Intralipid</td>
<td>52 (8)</td>
<td>54 (11)</td>
<td>48 (6)</td>
<td>66 (10)*</td>
</tr>
<tr>
<td>Coronary VR (dyne s⁻¹ cm⁻⁵)</td>
<td>Intralipid</td>
<td>2.3 (0.4)</td>
<td>2.6 (0.6)</td>
<td>2.2 (0.3)</td>
<td>1.6 (0.2)</td>
</tr>
<tr>
<td>Portal BF (ml min⁻¹)</td>
<td>Intralipid</td>
<td>379.2 (42)</td>
<td>405 (52)</td>
<td>387 (55)</td>
<td>360 (65)</td>
</tr>
<tr>
<td>Portal VR (dyne s⁻¹ cm⁻⁵)</td>
<td>Intralipid</td>
<td>0.28 (0.03)</td>
<td>0.27 (0.03)</td>
<td>0.28 (0.04)</td>
<td>0.27 (0.03)</td>
</tr>
<tr>
<td>Hepatic BF (ml min⁻¹)</td>
<td>Intralipid</td>
<td>69 (24)</td>
<td>127 (25)</td>
<td>96 (16)</td>
<td>108 (19)</td>
</tr>
<tr>
<td>Hepatic VR (dyne s⁻¹ cm⁻⁵)</td>
<td>Intralipid</td>
<td>1.25 (0.2)</td>
<td>1.08 (0.22)</td>
<td>1.5 (0.4)</td>
<td>1.0 (0.3)</td>
</tr>
<tr>
<td>Renal BF (ml min⁻¹)</td>
<td>Intralipid</td>
<td>89 (11)</td>
<td>102 (11)*</td>
<td>123 (34)</td>
<td>121 (29)</td>
</tr>
<tr>
<td>Renal VR (dyne s⁻¹ cm⁻⁵)</td>
<td>Intralipid</td>
<td>1.4 (0.24)</td>
<td>1.2 (0.17)</td>
<td>1.4 (0.48)</td>
<td>0.9 (0.2)</td>
</tr>
<tr>
<td>Vertebral BF (ml min⁻¹)</td>
<td>Intralipid</td>
<td>19 (2.5)</td>
<td>19 (1.8)</td>
<td>19 (4)</td>
<td>24.7 (7.6)</td>
</tr>
<tr>
<td>Vertebral VR (dyne s⁻¹ cm⁻⁵)</td>
<td>Intralipid</td>
<td>5.9 (0.7)</td>
<td>6.0 (0.7)</td>
<td>7 (2)</td>
<td>5.6 (1.4)</td>
</tr>
<tr>
<td>Mesenteric BF (ml min⁻¹)</td>
<td>Intralipid</td>
<td>99 (7)</td>
<td>93 (7)</td>
<td>117 (30)</td>
<td>103 (26)</td>
</tr>
<tr>
<td>Mesenteric VR (dyne s⁻¹ cm⁻⁵)</td>
<td>Intralipid</td>
<td>0.96 (0.03)</td>
<td>1.18 (0.11)*</td>
<td>1.0 (0.2)</td>
<td>1.0 (0.2)</td>
</tr>
<tr>
<td>Pulmonary artery pressure (mm Hg)</td>
<td>Intralipid</td>
<td>9 (3)</td>
<td>10 (3)</td>
<td>15 (2)</td>
<td>18 (3)</td>
</tr>
</tbody>
</table>
**Data analysis**

A paired t-test was performed to analyse the differences between baseline (before drug administration) and steady state (60 min after propofol and/or intralipid). Data obtained in control conditions and under propofol and intralipid were analysed using an analysis of variance (ANOVA) for repeated measures in each group. When differences were significant, multiple within-group comparisons to the steady-state value obtained before L-NMA injections were performed using Fisher’s t-test. In addition, when differences between control and propofol and/or intralipid at 60 min were significant, the magnitude of changes produced by L-NMA of each experimental condition was compared using an unpaired t-test. *P<0.05 vs steady state; **P<0.05 intralipid vs awake; †P<0.05 propofol vs awake; ‡P<0.05 intralipid vs propofol.

**Results**

Cardiac and regional haemodynamic values before propofol and intralipid administration are presented in Table 1. Baseline values were consistent with those previously reported for trained and unstressed animals and were not significantly different between groups. Changes in cardiac and regional haemodynamic parameters after propofol and intralipid administrations in the presence and absence of L-NMA are presented in Figures 1–4.

**Haemodynamic effects of propofol in an intralipid solution, and its solvent, intralipid**

As shown in Table 1, continuous infusion of propofol at 4 mg kg⁻¹, followed by 0.6 mg kg⁻¹ min⁻¹ over 60 min,
induced increases in HR and coronary BF and carotid BF and significant decreases in SVR and dP/dt. In contrast, intralipid increased renal BF and carotid and mesenteric VR.

**Effects of NOS inhibition using L-NMA on propofol- and intralipid-induced haemodynamic changes**

**Effects of L-NMA in control animals**

Systemic and regional haemodynamic parameters are presented in Figures 1–4. In Group 1, L-NMA induced brief transient increases in HR and dP/dt. It also produced an immediate and sustained increase in MAP and a decrease in CO, which resulted in an immediate and sustained systemic vasoconstriction. L-NMA also induced brief transient increases in carotid, coronary and vertebral BF. The transient increase in carotid BF was followed by a secondary decrease which lasted 60 min. Hepatic BF decreased at 5 min. Carotid and renal VR increased at 1 and 5 min, respectively, and remained elevated for 60 min, whereas Hep VR increased at 1 and 5 min only. Coronary VR decreased transiently at 1 min.

**Effects of propofol in an intralipid solution on NOS inhibition-induced haemodynamic changes**

In the presence of propofol and when compared with control experimental conditions, L-NMA produced a decrease in HR at 5–45 min and a more pronounced systemic vasoconstriction that lasted 10 min. The L-NMA-induced increases in carotid and vertebral BF and secondary decreases in carotid and vertebral were abolished. Finally, in these experimental conditions, L-NMA produced a brief secondary coronary vasoconstriction but no renal vasoconstriction.

**Effects of intralipid on haemodynamic changes induced by NOS inhibition**

In the presence of intralipid and when compared with control experimental conditions, L-NMA produced more
pronounced increases in MAP and SVR, and carotid vasoconstriction. No decreases in CO or increases in dP/dt were recorded. L-NMA also decreased HR at 15 and 45 min. L-NMA produced sustained decreases in renal BF at 10, 15 and 45 min and in mesenteric BF at 5–60 min, and more pronounced vasoconstriction in the carotid vasculature at 5–45 min, renal vasculature at 1-45 min and mesenteric vasculature at 1–60 min.

Comparison of the effects of L-NMA in the presence of propofol and intralipid indicated that in the presence of propofol, L-NMA produced a more pronounced decrease in HR at 15 and 45 min and a less pronounced carotid vasoconstriction.

**Discussion**

Plasma concentrations of propofol were not measured in our study. However, Goodchild and colleagues\(^{17}\) have previously shown that infusions of 0.33 and 0.66 mg kg\(^{-1}\) min\(^{-1}\) led to plasma concentrations of 2–13 µg ml\(^{-1}\) in dogs, which is within the anaesthetic range in humans. Thus, the propofol infusion rate used in our study most likely correlated with clinically relevant propofol concentrations.

Moreno and colleagues\(^{18}\) reported that *in vitro* propofol did not affect mesenteric vascular tone at concentrations \(<10^{-3}\)M. Brooke and colleagues\(^{19}\) reported that propofol does not affect renal BF *in vivo*. Although in our model propofol induced increases in carotid and coronary BF, it did not affect hepatic, portal, mesenteric, renal or vertebral BF. Therefore, our *in vivo* data confirm that propofol did not affect the mesenteric and renal circulations, and that the effects of propofol remain selective to regional circulation. Since intralipid did not affect either carotid or coronary BF, our data also suggest that the increases in coronary and carotid BF were specific to propofol and were not related to the presence of intralipid.

Our data also confirm that propofol induces a systemic vasodilatation associated with tachycardia and a decrease in
myocardial contractility. These effects on cardiac function were associated with an increase in carotid and coronary BF. Using a similar experimental design, Wouters and colleagues,20 Pagel and colleagues,1 and Moore and colleagues21 also reported an increase in coronary BF after propofol injected as a bolus. Yamanoue and colleagues22 and Gacar and colleagues5 demonstrated that, in vitro, propofol relaxes the coronary artery only at high concentrations. The short-lasting coronary vasodilatation was most likely indirect and related to the associated tachycardia via an increase in myocardial oxygen demand.

In assessing the role of the NO pathway in propofol-mediated haemodynamic changes, we hypothesized that: (i) the lack of difference in the effect induced by L-NMA in the presence of either propofol or intralipid compared with control indicated no interaction between the NO pathway and either propofol or intralipid; (ii) similar changes induced by L-NMA in the presence of both intralipid and propofol reflected an intralipid interaction; (iii) changes induced by L-NMA in the presence of either intralipid or propofol represented a propofol effect if recorded only in the presence of propofol, or represented opposite effects of intralipid and propofol if recorded only in the presence of intralipid.

Terragno and colleagues23 developed the concept that factors regulating regional BF vary according to experimental conditions. Our data indicate that in the presence of intralipid, the NO pathway plays a more important role in the local modulation of carotid, renal and mesenteric tone. Thus, in the presence of intralipid, the blockade of NOS resulted in more pronounced carotid, renal and mesenteric vasoconstriction as compared with control experimental conditions. Since propofol did not produce similar effects, it seems that the effects of propofol alone on the mesenteric and renal circulation are opposite to the effects produced by intralipid (i.e. propofol inhibited rather that stimulated the NO pathway). Indeed, in the presence of propofol the intralipid-mediated increased activity of NOS was abolished.

Furthermore, our data also confirm that the role of the NO pathway in the modulation of local circulation varies according to the territory. NO plays a minor role in the coronary circulation, whereas the role played by NOS in the carotid and renal circulations is more significant. However, our data support the concept that propofol inhibits rather than stimulates the NO pathway in these vascular beds. Thus, L-NMA produced similar carotid and renal vasoconstriction in control experimental conditions and in the presence of propofol whereas the renal and carotid vasoconstriction was accentuated in the presence of intralipid.

The effects of propofol and its solvent intralipid on the effects of L-NMA-associated changes in cardiac function are more complex. It is well established that under physiological conditions, the recorded increase in afterload produces a reflex-mediated decrease in HR and CO. L-NMA...
failed to increase HR initially in the presence of both propofol and intralipid. However, we recorded a secondary decrease in HR in the presence of both propofol and intralipid. Although CO remained unchanged in the presence of intralipid, changes in CO were similar in control experimental conditions and during propofol infusions. In these experimental conditions, CO did not decrease, suggesting that the presence of intralipid prevented the systemic vasoconstriction-mediated decrease in HR. The presence of intralipid also prevented the L-NMA-mediated decrease in CO, indicating an intralipid-related increase in venous return.

In summary, our data demonstrate that propofol produces selective regional haemodynamic changes. The stimulation of the NO pathway did not contribute to the regional changes mediated by propofol itself. This study also demonstrated that intralipid and not propofol stimulates the NO pathway.

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