# Direct Effects of Propofol on Myocardial Contractility in In Situ Canine Hearts 

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#### Abstract

The pronounced decrease in arterial blood pressure evident during anesthetic induction with propofol has raised the possibility that propofol has a direct negative inotropic effect. Previous attempts to evaluate this mechanism in vivo have been inconclusive because of confounding variables associated with intravenous administration of propofol. Accordingly, in the current study, steady-state changes in myocardial contractility and related hemodynamic parameters were assessed during intracoronary infusions of propofol in seven open-chest dogs anesthetized with fentanyl and midazolam. The left anterior descending coronary artery (LAD) was cannulated and perfused at controlled pressure ( 100 mmHg ) with normal arterial blood. In LAD-perfused myocardium, contractility was evaluated from measurements of percent segmental shortening (\%SS) obtained with ultrasonic crystals. Coronary blood flow in LAD was measured electromagnetically and used to calculate myocardial oxygen consumption ( $\mathrm{MV}_{\mathrm{O}_{3}}$; Fick principle) and coronary propofol concentration. Propofol was infused into the LAD at $150,300,600$, and 1,200 $\mu \mathrm{g} / \mathrm{min}$ ( $\mathbf{P}-150, \mathrm{P}-300, \mathrm{P}-600, \mathrm{P}-1,200$ ). These infusion rates yielded calculated blood concentrations of $7 \pm 1,15 \pm 1,26 \pm 2$, and $50 \pm 5$ $\mu \mathrm{g} \cdot \mathrm{ml}^{-1}$, respectively. The calculated blood concentrations at $\mathbf{P}-150$ were in the clinical range, whereas those at P-300, P-600, and P1,200 were supratherapeutic. P-150 had no effect on \%SS, whereas higher infusion rates caused decreases in \%SS. Changes in MV' $\mathbf{O}_{\mathbf{O}}$ by propofol generally paralleled changes in \%SS. At P-150 and P-300, coronary blood flow was proportional to $\mathrm{M}_{\mathrm{O}_{2}}$, whereas at P-600 and $P-1,200$, coronary blood flow was in excess of the prevailing $\mathbf{M} \dot{\mathbf{V}}_{\mathbf{O}_{\mathbf{2}}}$, resulting in increased coronary venous oxygen tension. In conclusion, propofol at clinically relevant blood concentrations has no direct negative inotropic effect in the in situ canine heart, although at supratherapeutic concentrations it causes cardiac depression. (Key words: Anesthetics, intravenous: propofol. Heart: coronary blood flow; myocardial contractility; myocardial oxygen consumption.)


[^0]Proporol (2,6-diisopropylphenol) is a new intravenous anesthetic agent that is used for both induction and maintenance of general anesthesia. ${ }^{1}$ The appeal of propofol stems from its favorable pharmacokinetic profile, including a high clearance rate and a relatively short elimination half-life. ${ }^{1}$

An undesirable side effect of induction of anesthesia with propofol is a pronounced decrease in arterial blood pressure. ${ }^{2}$ This response has raised the possibility that propofol has a direct negative inotropic effect. Previous studies evaluating this possibility in humans and experimental animals have yielded highly variable findings. ${ }^{3-8}$ This variability is likely attributable to factors associated with the intravenous administrations of propofol used in these studies. These factors include rapidly changing blood concentrations, varying cardiac loading conditions, and centrally mediated inhibition of the sympathetic nervous system. To avoid these potentially confounding variables, additional studies have been performed using isolated preparations of cardiac muscle or isolated perfused hearts. ${ }^{9,10}$ However, it is uncertain whether findings rendered from such in vitro studies have direct applicability to the normal intact heart.

Accordingly, the objective of the current study was to evaluate direct cardiac effects of propofol in in situ normally working canine hearts by use of selective intracoronary infusions. Measurements of segmental shortening, an index of myocardial contractility, were obtained by sonomicrometry and were correlated to changes in myocardial oxygen consumption and coronary blood flow. Because in the current study significant concentrations of propofol were confined to the coronary circulation, the complex systemic cardiovascular responses that complicated the interpretation of previous in vivo studies were avoided.

## Materials and Methods

## Canine Preparation

The study was conducted in compliance with the Institutional Animal Research Committee. Experiments were performed on nine conditioned, heartworm-free dogs of either sex (weight range $22-28 \mathrm{~kg}$ ). Anesthesia was induced with an intravenous bolus injection of thiopental in a dose of $15 \mathrm{mg} \cdot \mathrm{kg}^{-1}$. Anesthesia was maintained by continuous intravenous infusion of fentanyl and midazolam at rates of $12 \mu \mathrm{~g} \cdot \mathrm{~kg}^{-1} \cdot \mathrm{~h}^{-1}$ and 0.6
$\mathrm{mg} \cdot \mathrm{kg}^{-1} \cdot \mathrm{~h}^{-1}$, respectively. In some studies, small supplementary bolus injections of fentanyl were necessary to maintain the heart rate at 100 beats $\cdot \mathrm{min}^{-1}$. After tracheal intubation, the lungs were mechanically ventilated (Air Shields, Inc.) with the fractional inspired oxygen concentration equal to 1.0 . The volume and rate of the ventilator were established to maintain arterial carbon dioxide tension at a physiologic level. The oxygen tension, carbon dioxide tension, and $p \mathrm{H}$ of the arterial and coronary venous (see below) blood samples were measured electrometrically (model 1306, Instrumentation Laboratories, Lexington, MA). The hematocrit of blood samples was determined with a microcentrifuge. To facilitate artificial ventilation, muscle paralysis was obtained with an intravenous injection of vecuronium bromide $0.1 \mathrm{mg} \cdot \mathrm{kg}^{-1}$ with supplements of $0.05 \mathrm{mg} \cdot \mathrm{kg}^{-1} \cdot \mathrm{~h}^{-1}$. Body temperature was maintained at $38^{\circ} \mathrm{C}$ with a heating pad. Lactated Ringer's solution was administered continuously at a rate of $5 \mathrm{ml} \cdot \mathrm{kg}^{-1} \cdot \mathrm{~h}^{-1}$ intravenously to compensate for evaporative fluid losses. ${ }^{11}$

The heart was exposed through a left thoracotomy in the fourth intercostal space. Polyethylene cannulas were inserted into 1) the thoracic aorta via the right femoral artery for measuring arterial blood pressure, 2) the right brachial artery and vein for collecting samples of arterial blood for gas analysis and for infusing anesthetics, respectively, and 3) the vena cava (via the right femoral vein) for administration of heparin ( $400 \mathrm{U} \cdot \mathrm{kg}^{-1}$ with supplementation) for anticoagulation.

A micromanometer-tip pressure transducer (Millar Instruments, Houston, TX) was inserted into the left ventricle via the left atrium and mitral valve to measure left ventricular pressure. The maximum rate of increase of left ventricular systolic pressure ( $\mathrm{dP} / \mathrm{dt}_{\text {max }}$ ) was obtained
from the left ventricular pressure pulse with an electronic differentiator. Arterial blood pressure and coronary perfusion pressure were measured with Statham pressure transducers (model P231D, Gould, Cleveland, OH). A continuous record of blood pressures, left ventricular dP/ $\mathrm{dt}_{\text {max }}$, segmental shortening, and coronary blood flow (see below) was obtained on an eight-channel physiologic recorder (model 2800 S, Gould).

The left anterior descending coronary artery (LAD) was isolated approximately 2 cm from its origin for cannulation. A thin-wall stainless-steel cannula ( 2.5 mm inside diameter) was introduced into the isolated segment of the LAD, so that the artery could be perfused selectively by an extracorporeal perfusion system (fig. 1). Cannulation of the LAD required that blood flow was interrupted for less than 60 s , which resulted in a readily reversed, brief period of myocardial ischemia. The perfusion system used a reservoir ( $500-\mathrm{ml}$ aspirator bottle) that contained normal, well-oxygenated blood supplied by a peristaltic pump from the left femoral artery. The blood reservoir was connected to a large (20-1) air chamber that was pressurized with compressed air. Because of the large volume of the air chamber, small changes in the blood volume of the reservoir had negligible effect on coronary perfusion pressure. Coronary perfusion pressure was maintained equal to mean aortic pressure throughout the study.

The blood reservoir was connected to the LAD cannula with tubing. This tubing was equipped with 1) a heat exchanger to maintain the temperature of the blood perfusate temperature at $38^{\circ} \mathrm{C}, 2$ ) an electromagnetic flow transducer to measure coronary blood flow, 3) ports for collecting samples of coronary blood perfusate, for injecting radioactive microspheres, and for infusing agents, and 4) a mixing chamber to ensure dispersion of agents

Fig. 1. Extracorporeal perfusion system permitting selective infusion of propofol in the left anterior descending coronary artery (LAD) with perfusion pressure held constant.



FIG. 2. Original tracing demonstrating effects of intracoronary propofol, infused at $600 \mu \mathrm{~g} / \mathrm{min}$ on monitored hemodynamic parameters. At time A (arrow) the infusion was begun, and at time B (arrow) it was stopped. The reduction in segmental shortening by propofol was readily reversible, and it occurred in the presence of stable coronary perfusion pressure and systemic hemodynamic parameters. $\mathrm{dP} / \mathrm{dt}=\mathrm{rate}$ of change of pressure.
and microspheres administered into the coronary artery. LAD perfusion pressure was sensed through a small-diameter tube positioned at the orifice of the perfusion cannula. Lactated Ringer's solution was infused intravenously as necessary to maintain aortic pressure during filling of the extracorporeal perfusion system with arterial blood.

## Experimental Measurements

## Myocardial Segmental Shortening

Measurements of myocardial segmental length in the LAD bed were obtained by sonomicrometry. ${ }^{12}$ A pair of ultrasonic crystals were implanted into the LAD-perfused myocardium to a depth approximately midway between the epicardium and endocardium. Location in the LAD perfusion field and the function of the crystals were verified by segmental lengthening during a brief ( $30-\mathrm{s}$ ) occlusion. ${ }^{12}$ Changes in distance between the crystals were recorded from measurements of the ultrasonic transit time between the crystals (Triton Technology, San Diego, CA). The end-diastolic and end-systolic lengths were identified
by the beginning of the rapid increase in the left ventricular pressure just before isovolumetric contraction and the maximum rate of decrease of left ventricular systolic pressure ( $-\mathrm{dP} / \mathrm{dt}_{\text {max }}$ ), respectively (fig. 2). Percent segmental shortening, an index of myocardial contractility, was calculated from the formula:

$$
\% \mathrm{SS}=[(\mathrm{EDL}-\mathrm{ESL}) / \mathrm{EDL}] \times 100
$$

where $\%$ SS = percent segmental shortening; EDL = enddiastolic length; and ESL = end-systolic length.

## Myocardial Oxygen Consumption

The anterior interventricular vein was cannulated at the same level as was the LAD. The venous cannula was allowed to drain freely into a beaker to prevent venous stagnation and interstitial edema. This venous blood was returned intermittently to the dog to maintain isovolemic conditions. At specified times in the study, $1-\mathrm{ml}$ blood samples were collected from the coronary venous cannula under mineral oil to maintain anaerobic conditions. These
venous blood samples were paired with $1-\mathrm{ml}$ arterial blood samples obtained from the LAD perfusion tubing, so that the coronary arteriovenous oxygen difference could be determined.

Hemoglobin concentration and percent hemoglobin oxygen saturation of the coronary blood samples was measured with a CO-oximeter (model 482, Instrumentation Laboratories) and used to calculate the oxygen bound to hemoglobin, assuming the oxygen-carrying capacity of hemoglobin to be $1.39 \mathrm{ml} \mathrm{O}_{2} \cdot \mathrm{~g}^{-1} .^{13}$ The oxygen dissolved in the blood was computed ( $\mathrm{O}_{2}$ dissolved $=0.003$ $\mathrm{ml}^{\prime} \mathrm{O}_{2} \cdot 100 \mathrm{ml}$ blood $^{-1} \cdot \mathrm{mmHg}^{-1}$ ) and added to the bound component to compute total oxygen content. Myocardial oxygen consumption was calculated using the Fick principle, as the product of the coronary arteriovenous oxygen difference and the LAD blood flow (measured electromagnetically) at the time that blood samples were obtained.

## Transmural Distribution of Myocardial Blood Flow

Fifty thousand microspheres ( $15 \mu \mathrm{~m}$ ) labeled with a particular radionuclide (New England Nuclear Corp., Boston, MA; 3M Company, St. Paul, MN) were dispersed in a solution of $10 \%$ dextran and agitated in a vortex mixer and in an ultrasonic bath. These microspheres were injected into the perfusion tubing proximal to the mixing chamber to assess the transmural distribution of LAD perfusion. ${ }^{14}$ Microsphere injections were made under control conditions (no infusion of propofol) and during infusion of propofol at the rate of $600 \mu \mathrm{~g} \cdot \mathrm{~min}^{-1}$ (see Experimental Protocols, below).

At the completion of each experiment, Evans blue dye was injected into the LAD with perfusion pressure maintained at the normal level to identify the LAD perfusion field. After the heart was stopped with potassium chloride, it was removed, trimmed, and frozen to facilitate sampling. The dyed myocardium was excised and weighed so that electromagnetic blood flow could be expressed on a per 100 g basis. A $3-\mathrm{g}$ transmural sample of myocardium was obtained from the center of the LAD perfusion field. This sample was divided into halves to yield epicardial and endocardial samples, which were weighed. Radioactivity of the myocardial samples (in counts per minute) was measured with a $\gamma$ spectrometer equipped with a multichannel analyzer (model 1282-002, LKB, Turku, Finland). Isotope separation was accomplished by standard techniques of $\gamma$ spectroscopy with the aid of a microcomputer (model 91499-70; IBM, Boca Raton, FL). The endocardium:epicardium flow ratio was calculated using the equation:

$$
\begin{aligned}
& \text { Endo } / \text { Epi }=\text { endocardial } \cdot \text { tissue }\left(\mathrm{cpm} \cdot \mathrm{~g}^{-1}\right) / \\
& \text { epicardial tissue }\left(\mathrm{cpm} \cdot \mathrm{~g}^{-1}\right)
\end{aligned}
$$

where Endo/epi = endocardium:epicardium flow ratio, and $\mathrm{cpm}=$ counts per minute.

## Experimental Protocols

The direct cardiac effects of propofol were evaluated at four intracoronary infusion rates: $150,300,600$, and $1,200 \mu \mathrm{~g} \cdot \mathrm{~min}^{-1}$ in seven dogs. Propofol was diluted to $300 \mu \mathrm{~g} \cdot \mathrm{ml}^{-1}$ with $5 \%$ dextrose, resulting in a range of infusion rates between 0.5 and $4.0 \mathrm{ml} \cdot \mathrm{min}^{-1}$. Preliminary studies demonstrated that infusion of the dextrose vehicle alone at these low rates had no effect on monitored hemodynamic parameters, including segmental shortening and coronary blood flow. The coronary blood concentration of propofol agent was calculated by dividing the intracoronary infusion rate (in micrograms per minute) by the prevailing LAD blood flow rate (in milliliters per minute).

Initial control measurements were obtained after at least 30 min had been permitted for recovery from surgical preparation. Then, propofol was infused into the coronary artery with a syringe pump (Harvard Instruments, Boston, MA) at a site proximal to the mixing chamber. When stable values for monitored local hemodynamic parameters, e.g., segmental shortening and coronary blood flow, indicated steady-state conditions (610 min ), measurements were obtained again. This protocol was repeated for all four intracoronary infusion rates of propofol in each dog. The order of these intracoronary infusion rates was randomized in the seven dogs studied.

In two additional dogs, the propofol solvent, Intralipid, was diluted to the same concentration as propofol and infused separately into the LAD across an identical range of infusion rates, $0.5-4.0 \mathrm{ml} \cdot \mathrm{min}^{-1}$.

## Statistical Analysis

Student's $t$ test for paired samples ${ }^{15}$ was used to evaluate the effects of the intracoronary infusions on cardiac parameters. Changes in segmental shortening by propofol were normalized on the basis of percent of the control (or prepropofol) value. The findings at the variable rates of propofol infusion were compared using analysis of variance and the Student-Newman-Kuels test. ${ }^{15}$ A $P$ $<0.05$ was considered significant throughout this study.

## Results

Figure 2 shows a representative tracing of effects of intracoronary infusion of propofol at $600 \mu \mathrm{~g} \cdot \mathrm{~min}^{-1}$. At the point marked $A$ the infusion was begun, and at $B$ it was stopped. Propofol at $600 \mu \mathrm{~g} \cdot \mathrm{~min}^{-1}$ caused a significant reduction in segmental shortening (panel 1), which was readily reversible (panel 2). Coronary blood flow re-


Fig. 3. Summary of changes in regional segmental shortening and calculated coronary blood concentration for propofol as a function of intracoronary infusion rate of propofol.
mained near the control level. Of note was that coronary perfusion pressure and other monitored hemodynamic parameters were constant during intracoronary infusion of propofol.

Figure 3 summarizes the changes in regional segmental shortening as a function of the intracoronary infusion rate of propofol and also presents the calculated coronary blood concentration for propofol at each infusion rate. At an infusion rate of $150 \mu \mathrm{~g} \cdot \mathrm{~min}^{-1}$ (corresponding to a calculated blood concentration of $7 \pm 1 \mu \mathrm{~g} \cdot \mathrm{ml}^{-1}$ ), propofol had no effect on segmental shortening. Increasing the infusion rate to $300 \mu \mathrm{~g} \cdot \mathrm{~min}^{-1}$ resulted in a reduction in segmental shortening. This reduction in segmental shortening was greater at an infusion rate of 600 $\mu \mathrm{g} \cdot \mathrm{min}^{-1}$, but it did not increase further when the infusion rate was increased to $1,200 \mu \mathrm{~g} \cdot \mathrm{~min}^{-1}$.

Table 1 summarizes the changes in myocardial oxygen consumption and related parameters during graded intracoronary infusions of propofol. The prepropofol con-
trol values did not differ significantly. Therefore, for the sake of simplicity and brevity, table 1 presents the pooled mean for all controls. In general, the changes in myocardial oxygen consumption essentially mirrored the changes in segmental shortening. For example, propofol at 150 $\mu \mathrm{g} \cdot \mathrm{min}^{-1}$ did not change myocardial oxygen consumption, whereas at 300,600 , and $1,200 \mu \mathrm{~g} \cdot \mathrm{~min}^{-1}$ it caused a reduction in myocardial oxygen consumption. Coronary blood flow generally followed myocardial oxygen consumption at the lower doses of propofol. However, at 600 and $1,200 \mu \mathrm{~g} \cdot \mathrm{~min}^{-1}$ propofol, coronary blood flow was constant and increased, respectively, despite the reduction in myocardial oxygen consumption, thus raising local venous oxygen tension. Propofol did not alter the endocardium:epicardium flow ratio, which indicated that the modest flow changes observed were transmurally uniform.

Table 2 shows that selective intracoronary infusions of Intralipid had no significant effects on myocardial segmental shortening, myocardial oxygen consumption, or coronary blood flow in the LAD bed.

Table 3 presents mean control values for systemic hemodynamic parameters (mean aortic pressure, left ventricular pressure, left ventricular $\mathrm{dP} / \mathrm{dt}_{\text {max }}$, coronary perfusion pressure, and heart rate) as well as arterial blood gases in the nine dogs of the study. These values were in the normal range and remained constant during the course of each experiment, including during the selective intracoronary infusions of propofol and Intralipid.

## Discussion

## Critique of Methods

An extracorporeal perfusion system was used to investigate the direct cardiac effects of propofol in the in situ, normally working canine heart. This perfusion system has been used previously to evaluate direct cardiac effects of drugs, including the volatile anesthetic isoflurane, ${ }^{14,16}$ and physiologic factors, including hypoxemia and hemodilu-

|  | $\begin{aligned} & \text { Control } \\ & (\mathrm{n}=28) \end{aligned}$ | Propofol ( $\mu \mathrm{g} / \mathrm{min}$ ) |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: |
|  |  | $\begin{gathered} 150 \\ (\mathrm{n}=7) \end{gathered}$ | $\begin{gathered} 300 \\ (n=7) \end{gathered}$ | $\begin{gathered} 600 \\ (\mathrm{n}=7) \end{gathered}$ | $\begin{gathered} 1200 \\ (n=7) \end{gathered}$ |
|  |  | $5.8 \pm 0.5$ | $5.2 \pm 0.5 *$ | $5.3 \pm 0.4^{*}$ | $4.4 \pm 0.6$ * |
| $\operatorname{CBF}\left(\mathrm{ml} \cdot \min ^{-1} \cdot 100 \mathrm{~g}^{-1}\right)$ | $83 \pm 4$ | $74 \pm 6^{*}$ | $71 \pm 6^{*}$ | $82 \pm 7$ | $86 \pm 7^{*}$ |
| $\mathrm{Pv}_{\mathrm{O}_{2}}(\mathrm{mmHg})$ | $36 \pm 1$ | $35 \pm 2$ | $37 \pm 1$ | $39 \pm 1 *$ | $47 \pm 2.3^{*}$ |
| SS (\%) | $10.4 \pm 0.8$ | $10.0 \pm 1.3$ | $9.8 \pm 1.3 *$ | $7.8 \pm 1.7 *$ | $8.0 \pm 1.6^{*}$ |
| Endo/epi | $1.02 \pm 0.03$ | - | - | $1.14 \pm 0.06$ | - |

[^1]flow; $\mathbf{P v}_{\mathrm{O}_{\mathbf{2}}}=$ coronary venous oxygen tension; $\mathbf{S S}=$ segmental shortening; Endo/epi = endocardium/epicardium flow ratio.

* $P<0.05$, from paired control.

Table 2. Lack of Effect of Graded Intracoronary Infusions of Intralipid Alone on Myocardial Segmental Shortening and Related Variables

|  | Control$(n=8)$ | Intralipid ( $\mathbf{m l} \cdot \mathrm{min}^{-1}$ ) |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: |
|  |  | $\begin{gathered} 0.5 \\ (\mathrm{n}=2) \end{gathered}$ | $\begin{gathered} 1.0 \\ (n=2) \end{gathered}$ | $\begin{gathered} 2.0 \\ (n=2) \end{gathered}$ | $\begin{gathered} 4.0 \\ (n=2) \end{gathered}$ |
| SS (\%) | $13.5 \pm 2.0$ | $13.2 \pm 5.3$ | $14.2 \pm 5.3$ | $13.5 \pm 4.6$ | $13.5 \pm 4.6$ |
| $\mathrm{MV}_{\mathrm{O}_{2}}\left(\mathrm{ml} \cdot \min ^{-1} \cdot 100 \mathrm{~g}^{-1}\right)$ | $7.7 \pm 0.2$ | $7.7 \pm 0.5$ | $8.1 \pm 0.1$ | $7.2 \pm 0.4$ | $7.4 \pm 0.4$ |
| $\mathrm{CBF}\left(\mathrm{ml} \cdot \mathrm{min}^{-1} \cdot 100 \mathrm{~g}^{-1}\right)$ | $67 \pm 2$ | $70 \pm 2$ | $71 \pm 2$ | $66 \pm 2$ | $66 \pm 2$ |

Values are mean $\pm$ SE.
Abbreviations are as in Table 1.
tion. ${ }^{12,17}$ A limitation of this extracorporeal perfusion system is that pressure in the perfusion reservoir, in contrast to that in the aorta, is constant across the cardiac cycle. However, perfusion pressure in the LAD remains pulsatile (systolic pressure > diastolic pressure; fig. 2) because of the physical impediment to left coronary blood flow imposed by elevated subendocardial tissue pressures. ${ }^{18}$ This system results in control values for hemodynamic, metabolic, and functional variables in the perfused myocardium that are similar to those in the naturally supplied myocardium. Furthermore, vascular responsiveness is preserved, and vasodilator reserve remains normal. In the current study, the stability of the canine preparation was evidenced by the constancy of arterial blood and systemic hemodynamic variables, as well as of the control (prepropofol) values for variables in the LAD-perfused myocardium.

While the LAD was perfused with blood containing propofol, venous effluent containing propofol (that portion not collected via the implanted coronary venous catheter) returned directly to the systemic circulation and potentially could have recirculated and affected the myocardium. However, because of 1) the short duration of

Table 3. Control Values for Arterial Blood and Systemic Hemodynamic Variables

| Arterial blood variables |  |
| :---: | :---: |
| pH | $7.38 \pm 0.01$ |
| $\mathrm{P}_{\mathrm{CO}_{2}}(\mathrm{mmHg})$ | $36 \pm 1$ |
| $\mathrm{P}_{\mathrm{O}_{2}}(\mathrm{mmHg})$ | $258 \pm 21$ |
| Hemoglobin ( $\mathrm{g} \cdot 100 \mathrm{ml}^{-1}$ ) | $12.5 \pm 0.2$ |
| Oxygen saturation (\%) | $96 \pm 1$ |
| Oxygen content (vol\%) | $17.5 \pm 0.4$ |
| Hematocrit (\%) | $36 \pm 1$ |
| Systemic hemodynamic variables |  |
| MAP ( mmHg ) | $98 \pm 3$ |
| CPP (mmHg) | $101 \pm 1$ |
| LVEDP (mmHg) | $4.1 \pm 0.5$ |
| $\mathrm{LV} \mathrm{dP} / \mathrm{dt}_{\text {max }}\left(\mathrm{mmHg}^{\text {d }} \cdot \mathrm{s}^{-1}\right)$ | $1648 \pm 65$ |
| HR (beats $\cdot \mathrm{min}^{-1}$ ) | $102 \pm 5$ |

[^2]intracoronary administration of propofol, 2) the relatively small size of this coronary venous return compared to the total systemic venous return, and 3) the clearance of propofol via liver and kidney, we assumed that its concentrations in the systemic arterial circulation remained low. Although measurements of aortic blood concentrations were not available to confirm this assumption, two lines of evidence are consistent with such low concentrations. First, systemic hemodynamic parameters did not vary during the intracoronary infusion of propofol. Second, local cardiac effects of propofol rapidly reversed when the intracoronary infusions were stopped.

The location and orientation of the crystal pair were important considerations in using this sonomicrometric technique to evaluate local change in myocardial segmental shortening. Location within the LAD perfusion field was verified by demonstrating systolic bulging during a brief, 30 -s occlusion of the perfusion tubing. Furthermore, the crystals were oriented so that they were parallel with the anticipated direction of myocardial fibers in the left ventricular midwall. ${ }^{19}$ Although evaluations of myocardial contractility by measurements of segmental shortening have been shown to be sensitive to loading conditions of the heart, ${ }^{20}$ this limitation was not a factor in the current study because of the maintenance of constant hemodynamic conditions during the intracoronary infusions of propofol.

For the measurement of myocardial oxygen consumption to be valid, the blood samples from the anterior interventricular vein needed to be representative of the venous effluent from LAD-dependent myocardium. This condition was verified by previous studies that mapped left coronary venous drainage patterns using inert gas tracers ${ }^{21}$ or chromium-labeled red blood cells. ${ }^{22}$

The radioactive microsphere method can provide a reliable index of the transmural distribution of myocardial blood if 1 ) the injected microspheres themselves do not influence coronary hemodynamics; 2 ) the microspheres are well mixed in the coronary blood supply; 3) coronary arteriovenous shunting of microspheres is insignificant; and 4) at least 400 microspheres are present in tissue samples. ${ }^{23}$ With regard to the first condition, no changes in
coronary blood flow, measured electromagnetically, or in segmental shortening accompanied the intracoronary injection of the microspheres, implying unaltered local hemodynamic conditions. For the second, a previous study from this laboratory using identical intracoronary administrations of microspheres demonstrated that duplicate samples of blood withdrawn from the perfusion tubing differed by less than $5 \%$, indicating that microspheres were well mixed. ${ }^{14}$ For the third, the same study also demonstrated negligible radioactivity of local venous samples during intracoronary injections of microspheres, suggesting no significant arteriovenous shunting. ${ }^{14} \mathrm{Fi}$ nally, for the fourth, sufficient numbers of microspheres were recovered in all myocardial samples for low-error, high-precision estimates. Sample counts were accumulated to maintain statistical counting errors at less than $3 \%$.

General anesthesia was required in this open-chest canine preparation. An anesthetic technique composed of fentanyl and midazolam was used for several reasons. First, such techniques have been demonstrated by clinical investigators to be free of significant effects on cardiac function. ${ }^{24}$ Second, Flacke et al. ${ }^{25}$ reported that the combination of fentanyl and diazepam (another benzodiazepine) caused no additional cardiac depression in dogs anesthetized with enflurane after elimination of cardiac sympathetic drive with a spinal block. Finally, Reves et $a l .{ }^{26}$ found that excessive doses of fentanyl and diazepam together were required to depress isolated, perfused rat hearts, and that this effect occurred only in a strictly additive fashion. Noteworthy was that the use of combined fentanyl and midazolam for anesthesia in the current study produced a constant low heart rate, presumably reflecting a persistent reduction in sympathetic discharge to the heart.

Because measurements of myocardial contractility were not available in the dogs of the current study before induction of anesthesia, it was not possible to evaluate directly the effect of the background anesthetic on basal myocardial contractility or on the changes in myocardial contractility caused by intracoronary propofol. Thus, a contribution of this factor to the current findings cannot be totally discounted.

Propofol must equilibrate between the Intralipid liposomes and the serum proteins before it diffuses through the capillary wall. The time-course of these microkinetics is not known. Despite the use of a mixing chamber in the LAD perfusion line, propofol probably was present in the blood before it reached the coronary capillaries for a shorter time period during the intracoronary infusions than it is when administered intravenously. Thus, it cannot be ruled out that the available time for equilibration of propofol in the blood during the intracoronary infusions limited the delivery of propofol to the myocardium, with
the result that its negative inotropic effects were attenuated.

The lack of effect of the selective intracoronary infusions of Intralipid suggests that this solvent made no contribution to the myocardial effects observed during the intracoronary infusions of the propofol emulsion.

## Direct Cardiac Effects of Propofol

A meaningful comparison between the current findings and those of previous in vivo studies requires that equivalent blood concentrations for propofol be considered. Lepage et al. ${ }^{27}$ measured time-dependent changes in arterial blood concentrations for propofol after a standard bolus injection of $2 \mathrm{mg} \cdot \mathrm{kg}^{-1}$ followed by a maintenance infusion at $100 \mu \mathrm{~g} \cdot \mathrm{~kg}^{-1} \cdot \mathrm{~min}^{-1}$ in patients undergoing urologic surgery. The results demonstrated that propofol reached a peak concentration of $6.5 \mu \mathrm{~g} \cdot \mathrm{~m}^{-1} 1 \mathrm{~min}$ after bolus injection and declined rapidly thereafter. This peak arterial concentration was virtually identical to that calculated in the current study when propofol was infused intracoronarily at $150 \mu \mathrm{~g} \cdot \mathrm{~min}^{-1}$. Thus, an intracoronary infusion rate of $150 \mu \mathrm{~g} \cdot \mathrm{~min}^{-1}$ produced a clinically relevant blood concentration of propofol, whereas greater infusion rates produced supratherapeutic concentrations of propofol.

Intracoronary infusions of propofol at $150 \mu \mathrm{~g} \cdot \mathrm{~min}^{-1}$ caused no significant change in myocardial segmental shortening or oxygen consumption, suggesting the lack of a direct negative inotropic effect. This finding implies that direct cardiac depression contributes modestly if at all to the hypotensive response observed when propofol is used for anesthetic induction. The modest direct negative inotropic effect for propofol is consistent with a recent in vitro study conducted in isolated, perfused hearts. ${ }^{28}$ It is also consistent with findings from a recent study in which propofol was infused intravenously in dogs in which neurogenic regulation of the heart was abolished by combined bilateral vagotomy and $\beta$-adrenergic blockade. ${ }^{29}$ Additional support for the current findings is derived from a study in humans with artificial hearts, suggesting that the hypotensive action of propofol can be explained by its ability to relax vascular smooth muscle in both venous and arteriolar (resistance) vessels. ${ }^{8}$ A role for venodilation was also suggested by the recent report of an increase in forearm venous capacitance during steady-state infusions of propofol in humans. ${ }^{30}$ Such venodilation causes a reduction in preload and, in turn, cardiac output, whereas vasodilation causes a reduction in systemic vascular resistance.

Several previous investigators have reported a negative inotropic response during intravenous administration of propofol in both patients and laboratory animals. ${ }^{3-7} \mathrm{~A}$
definitive explanation for the apparent conflict between those findings and the results of the current study remains uncertain. However, one possible explanation may be the complicating influence of changing cardiac loading conditions on the indices of myocardial contractility used in these previous studies. Another possible explanation may be a reduction in sympathetic discharge to the heart by depression of the central nervous system during intravenous administration of propofol. The ability of propofol to inhibit the sympathetic nervous system has been suggested on the basis of blunted release of norepinephrine from sympathetic nerve terminals in dogs ${ }^{31}$ and reduced frequency of sympathetic nerve impulses in humans ${ }^{32}$ after anesthetic induction with propofol. Reduced activity of the cardiac sympathetic nerves because of depression of the central nervous system was not a factor in the current study because propofol was administered directly into the coronary circulation:

At the lower doses of propofol, the change in coronary blood flow generally paralleled that in myocardial oxygen consumption, suggesting intact metabolic regulation of myocardial perfusion. ${ }^{18}$ However, at the higher doses of propofol, the rate of coronary blood flow was in excess of the prevailing myocardial oxygen consumption, resulting in an increased coronary venous oxygen tension. These changes are consistent with direct dilation of coronary resistance vessels by propofol at high blood concentrations. ${ }^{18}$ This observation provides confirmation in the in situ heart for previous findings obtained in vitro in isolated rabbit hearts ${ }^{33}$ and in isolated coronary artery rings, ${ }^{34}$ suggesting a direct relaxing effect for propofol in the coronary circulation.

In summary, propofol at clinically relevant blood concentrations has no apparent direct cardiac effects in in situ, canine hearts, although it causes cardiac depression and coronary vasodilation at supratherapeutic blood concentrations. The current findings suggest that the hypotension occurring during anesthetic induction with propofol is not due to a direct negative inotropic effect. Another mechanism must be responsible, with possibilities including reduced sympathetic discharge to the heart and peripheral vasodilation and/or venodilation.

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[^1]:    Values are mean $\pm$ SE. Control values for Endo/epi obtained in 7 days.
    $\mathrm{MV}_{\mathrm{O}_{\mathbf{2}}}=$ myocardial oxygen consumption; $\mathrm{CBF}=$ coronary blood

[^2]:    Values are mean $\pm \mathrm{SE}$ in nine dogs $(\mathrm{n}=36)$.
    MAP = mean aortic pressure; CPP = coronary perfusion pressure; LVEDP = left ventricular end-diastolic pressure; LV dP/ $\mathrm{dt}_{\text {max }}=$ maximum rate of change of left ventricular pressure; $\mathrm{HR}=$ heart rate.

