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Negative Inotropic Effects of Propofol as Evaluated by the Regional Preload Recrutable Stroke Work Relationship in Chronically Instrumented Dogs

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Background: Propofol anesthesia often is associated with marked decreases in arterial blood pressure. Previous investigations *in vivo* have provided conflicting reasons for this clinical finding, including propofol-induced decreases in preload or afterload and/or direct myocardial depressant effects. Interpretation of the results of these studies is complicated by use of indices of myocardial contractility that may only indirectly indicate changes in inotropic state or are significantly dependent on ventricular loading conditions.

Methods: Eight experiments were performed using dogs chronically instrumented for measurement of aortic and left ventricular pressure, the peak rate of increase of left ventricular pressure (dP/dt_{max}), subendocardial segment length, intrathoracic pressure, and cardiac output. Myocardial contractility was evaluated in conscious and anesthetized dogs using the preload recruitable stroke work (PRSW) relationship, a sensitive, easily quantified, and relatively load-independent index of contractile function in normal canine myocardium *in vivo*. The relationship was derived from ventricular pressure-segment length loops generated by abrupt vena caval constriction. Respiratory variation in ventricular pressure was reduced by calculation of transmural pressure *via* instantaneous subtraction of intrathoracic pressure from corresponding left ventricular pressure. Systemic hemodynamics and myocardial contractility were recorded and evaluated in the conscious state and after a bolus of 5 mg/kg and a propofol infusion for 15 min at 15, 30, 60, and 120 mg · kg⁻¹ · h⁻¹.

Results: A significant ($P < .05$) and dose-dependent decrease in PRSW slope (106 ± 7 during control to 54 ± 3 mmHg at the 120 mg · kg⁻¹ · h⁻¹ infusion) was observed, demonstrating a di-

rect depression of contractility. Concomitant decreases in left ventricular dP/dt_{max} and percent segment shortening also were observed. In addition, a significant decrease in systemic vascular resistance occurred at the two largest infusions.

Conclusions: The results indicate that the significant decrease in systemic arterial blood pressure observed during continuous propofol anesthesia in dogs is a result of direct negative inotropic actions of propofol along with its direct effects upon arterial and venous vascular tone. (Key words: Anesthetics, intravenous: propofol. Heart: coronary hemodynamics; left ventricular function; myocardial contractility; preload recruitable stroke work; systemic hemodynamics.)

INDUCTION or maintenance of anesthesia with propofol (2,6 diisopropylphenol) frequently is associated with significant decreases in systemic arterial blood pressure.¹⁻⁸ The etiology of propofol-induced hypotension remains controversial despite extensive study. Several investigations have suggested that the circulatory depression observed with propofol can be attributed to either veno- or arterial vasodilation and subsequent decreases in left ventricular preload or afterload with relative sparing of global myocardial function.^{2-5,9-14} In contrast, other studies have implied that propofol may produce direct myocardial depression, which plays a major role in the decreases in arterial blood pressure observed during propofol anesthesia.^{6,14-20} This latter conclusion requires qualification, however, because several previous investigations *in vivo* used assays of myocardial contractility that only indirectly indicate changes of inotropic state or are dependent on ventricular loading conditions (*e.g.*, ejection fraction, cardiac output and left ventricular peak positive dP/dt). Other studies have used relatively load-independent techniques derived from pressure-dimension loops (end systolic pressure-dimension relations, ESPDR) to measure propofol-induced changes in contractility.^{6,15,16} These investigations supported the contention that propofol produced direct myocardial

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depression, however, strict interpretation of the results of these studies is obscured substantially by significant difficulties with methodology. In addition, ESPDR-derived contractile indices may manifest loss of linearity and relative insensitivity to decreases in contractile state at lower ranges of systemic arterial pressure²¹⁻²⁴ similar to those that may be encountered with administration of propofol administration. Thus, conclusions about the relative contribution of propofol-induced negative inotropic effects to the observed decreases in blood pressure in response to the administration of this drug have not been established firmly.

The purpose of this investigation was to reexamine the direct effects of propofol on regional myocardial contractility in chronically instrumented dogs. Contractile state was assessed using the preload recruitable stroke work (PRSW) relationship. This technique is a linear extension of the traditional Frank-Starling concept and has been shown to be a heart rate- and load-independent, easily quantified assay of regional inotropic state in conscious and anesthetized dogs.^{25,26} Changes in contractile state derived from ventricular pressure-regional dimension loops have been shown to closely approximate alterations in global ventricular performance in normal myocardium *in vivo*.²⁶⁻²⁸ In addition, the PRSW relationship, which incorporates data from the entire cardiac cycle, may maintain improved linearity and sensitivity to change in contractile state at lower ranges of systemic arterial blood pressure, offering potentially important advantages over other indices of contractility derived from ventricular pressure-dimension loops.²¹ Thus, the effects of total intravenous (iv) anesthesia with propofol on myocardial contractility were evaluated using a sensitive and load-independent measure that quantitatively described propofol-induced changes in contractility. Chronically instrumented dogs were used so that comparisons could be made directly to the conscious state.

Methods

All experimental procedures and protocols used in this investigation were reviewed and approved by the Animal Care Committee of the authors' institution. Furthermore, all conformed to the *Guiding Principles in the Care and Use of Animals of the American Physiologic Society* and were in accordance with the *Guide for the Care and Use of Laboratory Animals* [DHEW (DHHS) publication no. (NIH) 85-23, revised 1985].

General Preparation

Surgical implantation of instruments has been described in detail elsewhere.^{20,25} Under general anesthesia and aseptic conditions, a thoracotomy was performed in the left fifth intercostal space. Heparin-filled catheters were placed in the descending thoracic aorta and the right atrium for determination of aortic blood pressure and fluid or drug administration, respectively. An ultrasonic flow probe (Transonics, Ithaca, NY) was positioned around the ascending thoracic aorta for measurement of relative cardiac output (minus coronary blood flow). A pair of miniature ultrasonic segment length transducers (5 MHz) for determination of regional contractile function (segment shortening) were implanted within the subendocardium in the free wall of the left ventricle in the perfusion territory of the left anterior descending coronary artery in each dog to minimize differences in regional function known to occur in different areas of the heart. A high-fidelity, miniature micromanometer (P7, Konigsberg Instruments, Pasadena, CA) was implanted in the left ventricle for measurement of left ventricular pressure and the maximum rate of increase of left ventricular pressure (dp/dt_{max}). A heparin-filled catheter was inserted into the left atrial appendage, and the left ventricular micromanometer was cross-calibrated *in vivo* against pressures measured *via* arterial and left atrial catheters (Gould P₅₀ pressure transducer, Oxnard, CA). A single-port 16-G heparin-filled catheter was placed in the apex of the left thoracic cavity between the lung and chest wall through the thoracotomy incision for subsequent measurement of continuous intrathoracic pressure.^{29,30} A 1.5–2-cm segment of proximal left anterior descending coronary artery was isolated, and a precalibrated Doppler ultrasonic flow transducer was placed around this vessel for determination of diastolic coronary blood flow velocity. Typical waveforms are seen in figure 1. Lastly, a hydraulic vascular occluder (In Vivo Metric[†], Healdsburg, CA) was placed around the thoracic inferior vena cava for abrupt alteration of left ventricular preload. All instrumentation was secured, tunneled between the scapulae, and exteriorized *via* several small incisions. The pericardium was left open, the chest wall closed in layers, and the pneumothorax evacuated by a chest tube. Each dog was fitted with a jacket (Alice King Chatham, Los Angeles, CA) to prevent damage to the instruments and catheters that were contained in an aluminum box within the jacket pocket.

After surgery, each dog (N = 8) was treated with analgesics as needed (0.02 mg/kg intramuscular bu-

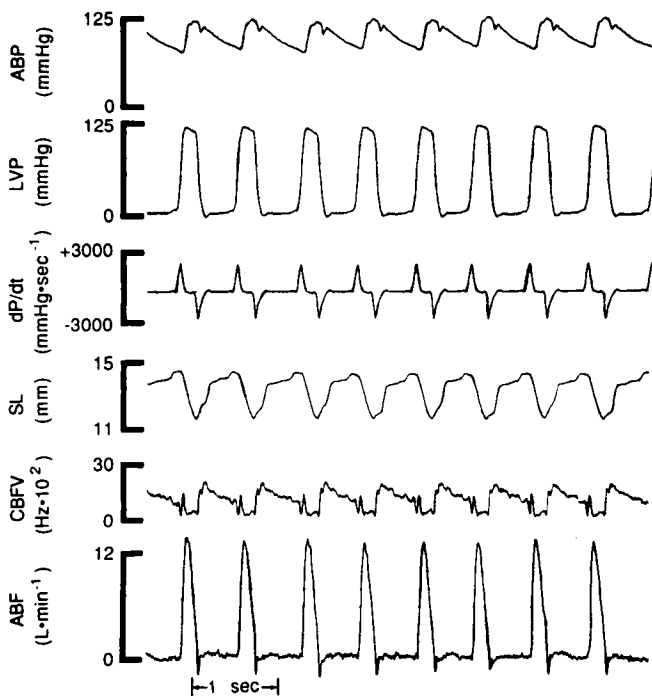


Fig. 1. Continuous aortic blood pressure (ABP), left ventricular pressure (LVP), dP/dt , segment length (SL), coronary blood flow velocity (CBFV), and aortic blood flow (ABF) waveforms obtained during a typical experiment.

prenorphine). Antibiotic prophylaxis consisted of procaine penicillin G (25,000 U/kg) and gentamicin (4.5 mg/kg). Dogs were allowed to recover for a minimum of 10 days prior to experimentation. During the post-operative period, dogs were trained to stand quietly in a sling during hemodynamic monitoring. Segment length and coronary blood flow velocity signals were driven and monitored by ultrasonic amplifiers (Hartley, Houston, TX). End systolic segment length (ESL) was measured at maximum negative left ventricular dP/dt , and end diastolic segment length (EDL) was measured immediately before the onset of left ventricular isovolumetric contraction. The lengths were normalized according to the method described by Theroux *et al.*³¹ Percent segment shortening (%SS) was calculated by use of the equation: $\%SS = (EDL - ESL) \cdot 100 \cdot EDL^{-1}$. Relative diastolic coronary vascular resistance was calculated as the quotient of diastolic arterial pressure and diastolic coronary blood flow velocity ($\text{Hz} \times 10^2$). All hemodynamic data were continuously recorded on a Hewlett Packard 7758A polygraph (San Francisco, CA) and digitized *via* a computer interfaced with an analog-to-digital converter.

Experimental Protocol

All dogs (24.2 ± 0.7 kg, mean \pm SEM) were fasted overnight, and fluid deficits were replaced before experimentation with crystalloid (500 ml lactated Ringer's solution). Maintenance fluids were continued at $3 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ (lactated Ringer's solution) for duration of each experiment. The instrumentation was calibrated and baseline systemic hemodynamics were recorded continuously for 30 min. Abrupt alteration of preload *via* inflation of the inferior vena caval hydraulic vascular occluder was used to generate left ventricular pressure-segment length loops used for analysis of myocardial contractility. Continuous ventricular pressure, segment length, and intrathoracic pressure waveforms were recorded on a digital oscilloscope (Model 4094C, Nicolet Instruments, Madison, WI) in the conscious state. The inferior vena cava was abruptly occluded to reduce left ventricular systolic pressure approximately 30 mmHg over 10–20 cardiac cycles (6–8 s). Ventricular pressure-segment length loops were rejected if the heart rate increased more than 10% above baseline levels during the occlusion. In this case, ventricular pressure-segment length loops were repeated after steady-state hemodynamics had been reestablished. Respiratory variation in ventricular pressure in the conscious state was later reduced off-line by electronic subtraction of the continuous intrathoracic pressure waveform from the left ventricular pressure waveform using the digital oscilloscope. The resultant left ventricular transmural pressure-segment length loops were used to evaluate myocardial contractility in the conscious state (fig. 2).

Induction of anesthesia was accomplished with propofol (5 mg/kg) *via* iv bolus. Following tracheal intubation, anesthesia was maintained with a propofol infusion at 15, 30, 60, or $120 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ in a random fashion. During anesthesia the lungs were mechanically ventilated with a nitrogen (75%) and oxygen (25%) mixture. After 15 min of equilibration at each propofol infusion rate, systemic hemodynamics were recorded and transmural pressure-segment length loops were obtained in the manner described above. The propofol infusion rate was then changed, and measurements were repeated after similar equilibration. Arterial blood gases were maintained at conscious levels by adjustment of nitrogen and oxygen concentrations and respiratory rate throughout the experiment.

Left ventricular transmural pressure-segment length loops (consisting of 10–20 cardiac cycles) were obtained under steady-state hemodynamic conditions in

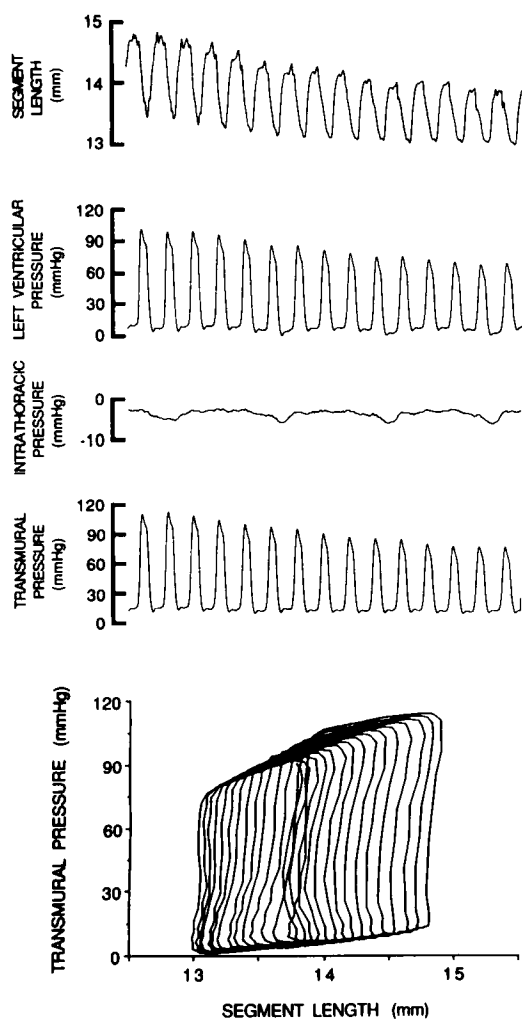
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Fig. 2. Continuous left ventricular pressure, segment length, intrathoracic pressure, and transmural pressure waveforms obtained during abrupt occlusion of the inferior vena cava in a typical experiment. Transmural pressure was generated by subtraction of continuous intrathoracic pressure from ventricular pressure, and transmural pressure-segment length loops were used to evaluate myocardial contractility with the preload recruitable stroke work (PRSW) relationship (see text).

the conscious state and during each propofol infusion. The area of each loop, corresponding to segmental stroke work (SW), was calculated by electronic integration. The EDL of each loop was identified on the oscilloscope and converted to the appropriate units (mm) by use of a linear formula generated with voltage-segment length calibration data. The segmental SW was then plotted against the corresponding EDL for each loop, and a linear regression analysis was used to describe the SW *versus* EDL slope (M_w) and length intercept (L_w): $SW = M_w(EDL - L_w)$.

Statistical Analysis

Statistical analysis of data during the conscious state and during all anesthetic interventions was performed by an analysis of variance (ANOVA) with repeated measures followed by application of Bonferroni's modification of the *t* test.³² Changes from control and anesthetic interventions were considered statistically significant when $P < .05$. The PRSW relationship (M_w and L_w) was described using a linear regression analysis. All data are expressed as mean \pm SEM.

Results

The effects of various doses of propofol on systemic and coronary hemodynamics and on ventricular function are summarized in table 1. A small increase in arterial oxygen tension was observed in all anesthetized dogs whose lungs were ventilated using positive pressure. Propofol caused significant ($P < .05$) increases in heart rate and dose-dependent decreases in mean arterial pressure and left ventricular systolic pressure. Decreases in left ventricular end diastolic pressure and EDL also were observed consistent with decreased preload, which occurred despite administration of crystalloid. Cardiac output was maintained at conscious levels during administration of propofol except at the highest dose. Significant decreases in systemic vascular resistance occurred at the 60 and 120 $mg \cdot kg^{-1} \cdot h^{-1}$ doses of propofol. No changes in diastolic coronary blood flow velocity were observed during propofol anesthesia. Calculated diastolic coronary vascular resistance decreased significantly at the two highest infusion rates.

Propofol produced a significant and dose-dependent decrease in myocardial contractility (fig. 3, table 1) as assessed with M_w (106 ± 7 mmHg during the conscious control to 54 ± 3 mmHg during the 120 $mg \cdot kg^{-1} \cdot h^{-1}$ propofol infusion). Regression coefficients obtained in the calculation of the PRSW *versus* EDL relationship were $r^2 \geq 0.97$ in the conscious and anesthetized states. No changes in L_w occurred during administration of propofol, suggesting that declines in contractility were not manifested by diastolic creep (increases in L_w). Concomitant declines in left ventricular dP/dt_{max} ($2,520 \pm 200$ during the conscious control to $1,310 \pm 120$ mmHg/s during the 120 $mg \cdot kg^{-1} \cdot h^{-1}$ propofol infusion) occurred, which may be consistent with a direct global myocardial depressant effect (fig. 1). In addition, regional contractility as assessed by %SS (a contractile index that also is influenced by heart rate

Table 1. Systemic and Coronary Hemodynamics during Propofol Anesthesia

| | Conscious | Propofol Infusion ($\text{mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) | | | |
|--|-------------|--|--------------|----------------|----------------|
| | | 15 | 30 | 60 | 120 |
| HR (beats/min) | 88 ± 3 | 134 ± 8* | 124 ± 9* | 122 ± 7* | 123 ± 8* |
| MAP (mmHg) | 96 ± 5 | 92 ± 7 | 79 ± 6*† | 64 ± 4*†§ | 58 ± 3*†§ |
| LVSP (mmHg) | 129 ± 6 | 115 ± 9* | 101 ± 8*† | 87 ± 5*†§ | 83 ± 4*†§ |
| LVEDP (mmHg) | 8 ± 1 | 6 ± 1* | 5 ± 1* | 5 ± 1* | 5 ± 1* |
| dP/dt _{max} (mmHg · s ⁻¹) | 2520 ± 200 | 2040 ± 210* | 1790 ± 170* | 1460 ± 130*†§ | 1310 ± 120*†§ |
| DCBFV (Hz · 10 ²) | 42.8 ± 4.9 | 39.8 ± 5.1 | 40.0 ± 5.5 | 40.2 ± 5.7 | 41.1 ± 6.2 |
| DCVR (units) | 2.02 ± 0.19 | 2.19 ± 0.20 | 1.85 ± 0.16† | 1.50 ± 0.16*†§ | 1.33 ± 0.15*†§ |
| CO (L · min ⁻¹) | 3.5 ± 0.6 | 3.3 ± 0.5 | 3.1 ± 0.6 | 3.1 ± 0.6 | 2.9 ± 0.6* |
| SVR (dyne · s · cm ⁻⁵) | 2580 ± 380 | 2580 ± 390 | 2340 ± 360 | 1970 ± 290*† | 1950 ± 310*† |
| SV (ml) | 41 ± 7 | 26 ± 3* | 25 ± 3* | 25 ± 8* | 24 ± 5* |
| SS (%) | 16.6 ± 1.4 | 13.5 ± 1.4* | 13.3 ± 1.7* | 13.1 ± 1.7* | 12.4 ± 1.6* |
| EDL (mm) | 15.7 ± 1.5 | 14.6 ± 1.4* | 14.6 ± 1.5* | 14.6 ± 1.4* | 14.8 ± 1.4* |
| ESL (mm) | 13.1 ± 1.2 | 12.5 ± 1.2* | 12.6 ± 1.2 | 12.7 ± 1.3 | 13.0 ± 1.3 |
| M _w (mmHg) | 106 ± 7 | 82 ± 6* | 72 ± 4*† | 64 ± 4*†§ | 54 ± 3*†‡§ |
| L _w (mm) | 12.6 ± 1.2 | 12.2 ± 1.1 | 12.2 ± 1.1 | 12.7 ± 1.1 | 12.9 ± 1.2 |

All data are mean ± SEM (n = 8). HR = heart rate; MAP = mean arterial pressure; LVSP and LVEDP = left ventricular systolic and end-diastolic pressure, respectively; DCBFV and DCVR = diastolic coronary blood flow velocity and vascular resistance, respectively; CO = cardiac output; SVR = systemic vascular resistance; SV = stroke volume; SS = segment shortening; EDL and ESL = end-diastolic and systolic segment length, respectively; M_w and L_w = preload recruitable stroke work versus end-diastolic segment length slope and length intercept, respectively.

* Significantly ($P < .05$) different from conscious.

† Significantly ($P < .05$) different from 15 $\text{mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ propofol infusion.

§ Significantly ($P < .05$) different from 30 $\text{mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ propofol infusion.

‡ Significantly ($P < .05$) different from 60 $\text{mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ propofol infusion.

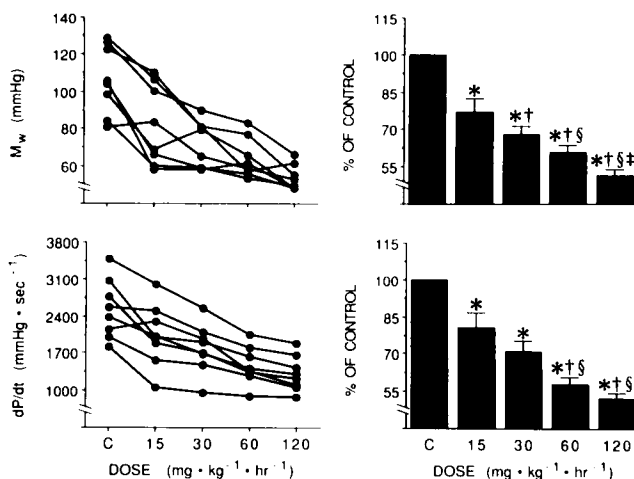


Fig. 3. Preload recruitable stroke work slope (M_w; top left) and left ventricular dP/dt (bottom left) for each dog and cumulative data represented as a percent of control (top and bottom right, respectively) during control (C) and at 15-, 30-, 60-, and 120- $\text{mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ infusions of propofol. *Significantly ($P < .05$) different from control. †Significantly ($P < .05$) different from 15- $\text{mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ propofol infusion. §Significantly ($P < .05$) different from 30- $\text{mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ propofol infusion. ‡Significantly ($P < .05$) different from 60- $\text{mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ propofol infusion.

and ventricular loading conditions) decreased significantly, although this effect was not dose-related.

Discussion

The direct effects of propofol on myocardial contractility *in vivo* remain controversial despite extensive study. LePage *et al.*⁴ demonstrated that neither ejection fraction nor end systolic volume were altered during the administration of propofol as evaluated using radionuclide ventriculography in patients with coronary artery disease, indirectly indicating a relative maintenance of left ventricular performance. Propofol produced no significant changes in cardiac output or stroke volume when administered as an induction agent to patients undergoing total hip replacement² or myocardial revascularization.^{3,5} Boer *et al.*⁹ and Rouby *et al.*¹⁰ demonstrated that propofol caused profound peripheral vascular dilation that contributed to declines in mean arterial blood pressure in patients whose cardiac output was controlled with cardiopulmonary bypass or artificial hearts, respectively. Most recently, Muzi *et al.*¹³ reported that propofol-induced hypotension also

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appeared to be mediated to a large degree by venodilation in human volunteers. These studies inferred that the hemodynamic depression observed with propofol could be attributed primarily to alterations in peripheral arterial or venous tone with relative maintenance of global myocardial function.

Other investigations *in vivo*, in contrast, have implied that propofol may produce direct myocardial depression. Mulier *et al.*¹⁵ used transesophageal echocardiography and peripheral arterial blood pressure to calculate an approximation of the end systolic pressure-volume relationship (ESPVR) in patients undergoing elective surgery and reported that propofol produced a significant decrease in the slope of the ESPVR (E_{es}), suggesting a direct negative inotropic effect. Gauss *et al.*⁶ also used an end systolic quotient derived using similar noninvasive parameters and demonstrated that induction doses of propofol appeared to decrease inotropic state in previously anesthetized volunteers. Interpretation of the results of these studies^{6,15} requires a substantial qualification,³³ however, because of several major limitations in methodology including: absence of correlation between peak systolic radial artery pressure and left ventricular end systolic pressure; lack of a precise definition of end systole, an important component in the calculation of the ESPVR;³⁴ assumption of a constant ESPVR volume intercept (V_0), a variable that changes with loading conditions or alterations in contractile state;^{35,36} and lastly, assumption of a linear relationship of the ESPVR despite previous demonstration of the curvilinearity and afterload dependence of this relationship, especially at lower ranges of arterial blood pressure.²²⁻²⁴ Coetzee *et al.*¹⁶ used ventricular pressure-segment length loops to derive the end systolic pressure-length relationship (E_{es}) and demonstrated that graded increases in plasma concentrations of propofol (0–7.73 $\mu\text{g}/\text{ml}$) resulted in progressive declines in myocardial contractility in acutely instrumented swine. In addition, calculated effective arterial elastance remained constant, suggesting that propofol was exerting primarily myocardial depressant actions without substantial effect on this measure of left ventricular afterload. The results of this investigation¹⁶ require qualification, however, because of concomitant administration of halothane, the presence of baseline tachycardia in an acute animal preparation, and, importantly, the failure of E_{es} to return to baseline control levels after the discontinuation of the propofol infusion. Other studies from this²⁰ and other laboratories^{14,17} also have provided indirect evidence

to support the contention that propofol-induced hypotension is mediated principally by depression of myocardial function.

Several investigations *in vitro* have supported the contention that propofol produces direct negative inotropic actions, however, some controversy concerning this conclusion remains as well. Preliminary reports in isolated rat ventricular septum,³⁷ guinea pig papillary muscle,³⁸ and rabbit papillary muscle³⁹ suggested that propofol results in declines in intrinsic contractility. Park and Lynch⁴⁰ compared effects of propofol and thiopental on mechanical function of isolated guinea pig ventricular muscle and reported that propofol produced dose-dependent myocardial depression that was significantly less than that produced with thiopental when clinical plasma concentration ranges required for equivalent anesthetic effect were compared. Stowe *et al.*,⁴¹ however, suggested that negative inotropic actions of propofol were similar to those of thiopental in isolated guinea pig hearts. In direct contrast, Riou *et al.*⁴² demonstrated that propofol produced little effect on intrinsic myocardial contractility in rat papillary muscle, results that suggested that the cardiovascular depression observed with propofol *in vivo* was not related to intrinsic myocardial depression.

The present investigation reexamined the effects of propofol on myocardial contractility using a relatively heart rate- and load-insensitive, easily quantified index of contractile state *in vivo*.^{25,26} The PRSW relationship was chosen as an assay of ventricular performance because this technique integrates data from the entire cardiac cycle (instead of relying on data obtained at an instantaneous definition of end systole) and has been shown to closely reflect global ventricular performance in normal canine myocardium *in vivo* when calculated using regional measures of function.²⁶ In addition, the PRSW relationship may be more reproducible than other measures of left ventricular contractile performance derived from pressure-volume loops (in contrast to the ESPVR or the dP/dt_{max} -end diastolic volume relationship) and may maintain improved linearity and quantitative sensitivity to changes in contractile state at low ranges of arterial blood pressure than other measures of inotropic state.²¹ A chronically instrumented dog model was used to avoid the confounding influences of acute surgical intervention and concomitant anesthetic administration.

The results of this investigation demonstrate that propofol causes a dose-dependent depression of myocardial contractility in chronically instrumented dogs.

The PRSW slope decreased approximately 23%, 32%, 39%, and 48% (change from the conscious state) when propofol was administered at infusion rates of 15, 30, 60, and 120 mg · kg⁻¹ · h⁻¹, respectively. Concomitant decreases in left ventricular dP/dt_{max} and %SS, indices of global and regional myocardial contractility that are significantly affected by heart rate and ventricular loading conditions,⁴⁵ also were observed, suggesting a depression of contractile function as well. This depression of myocardial function occurred despite a significant (but not dose-related) increase in heart rate, an alteration that would be expected to directly increase intrinsic contractility (treppe). The PRSW slope has been shown to be relatively independent of changes in heart rate²⁶; nonetheless, propofol may be producing an even greater level of myocardial depression if M_w was specifically corrected for observed increases in heart rate. Although the PRSW relationship has been shown to be relatively afterload insensitive, interpretation of decreases in contractility must be qualified because decreases in afterload (as indirectly assessed by systemic vascular resistance) were observed at the 60- and 120-mg · kg⁻¹ · h⁻¹ doses of propofol. These propofol-induced declines in systemic vascular resistance also may explain the relative maintenance of cardiac output that occurred despite dose-dependent decreases in M_w. The depression of contractility produced by propofol probably occurred independent of coronary blood flow as no changes in diastolic coronary blood flow velocity were observed in this investigation. The magnitude of the negative inotropic action observed with the 30-mg · kg⁻¹ · h⁻¹ dose of propofol is comparable to that produced by 1.0 MAC isoflurane (end tidal concentration) assessed using the same technique in a previous report⁴⁴ from this laboratory.

The results of this investigation confirm and extend the findings of Coetzee *et al.*¹⁶ in swine and Mulier *et al.*¹⁵ and Gauss *et al.*⁶ in humans and support the majority of recent evidence that propofol depresses myocardial contractility *in vitro*.³⁷⁻⁴¹ The results suggest that the significant decreases in systemic arterial blood pressure observed with continuous propofol anesthesia can be attributed to a combination of the direct negative inotropic actions of this drug along with the effects of this agent on peripheral arterial and venous vascular tone in dogs. Propofol decreased left ventricular afterload as indirectly assessed by systemic vascular resistance at the higher infusion rates. In addition, modest venodilation and decreases in preload manifested by declines in left ventricular end diastolic pressure and

EDL (which were not dose-related and occurred despite crystalloid administration during each experiment) were observed with propofol, which also may have contributed to decreases in systemic arterial blood pressure. These observations are supported by the findings of Goodchild and Serrao¹² in dogs and LePage *et al.*,⁴ Van Aken *et al.*,⁷ and Muzi *et al.*¹³ in humans. In contrast, however, propofol anesthesia resulted in significant increases in heart rate in the current investigation. Although propofol-induced tachycardia has been reported in patients with coronary artery disease,^{5,45} stability of heart rate during induction and/or maintenance of propofol anesthesia typically is described in humans because central sympatholytic and/or vagotonic effects⁴⁶ occur during propofol administration despite decreases in systemic arterial blood pressure. Therefore, extension of the findings of the current investigation in chronically instrumented dogs to the clinical setting must be approached with caution.

The doses of propofol used in this investigation were chosen specifically to provide reliable anesthesia in all dogs. Although plasma concentrations of propofol were not measured in this study, Goodchild and Serrao¹² have shown previously that infusions of 20 and 40 mg · kg⁻¹ · h⁻¹ produced plasma concentrations of 2–13 µg/ml in dogs, which are within the anesthetic range in humans. Thus, the 15- and 30-, and perhaps the 60-, mg · kg⁻¹ · h⁻¹ infusions of propofol used in this investigation may correlate with clinically relevant propofol concentrations. However, since plasma concentrations of propofol were not specifically obtained, direct comparison of the effect of this agent on systemic hemodynamics and myocardial contractility between the chronically instrumented canine model and humans can be inferred only indirectly.

In summary, the present investigation has shown that propofol produces dose-dependent and easily quantified decreases in myocardial contractility when administered as total iv anesthesia to chronically instrumented dogs. Propofol-induced depression of contractile function represents an important contributing factor to the depression of systemic arterial blood pressure observed during administration of this agent in dogs.

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