ventilating parts of the lung. Acta Physiol Scand [Suppl] 11:1–92, 1942
17. Schwartz D: Méthodes Statistiques à l'Usage des Médecins et des Biologistes. Paris, Flammarion, 1963, pp 245–257
18. Greene R, Zapol WM, Snider MT, Reid LM, Snow R, O'Connel RS, Novelline RA: Early bedside detection of pulmonary vascular occlusion during respiratory failure. Am Rev Respir Dis 124:591–601, 1981
19. Fozard JR: Mechanism of the hypotensive effect of ketanserin. J Cardiovasc Pharmacol 4:829–838, 1982
20. Olson NC: Role of 5-hydroxytryptamine in endotoxin-induced respiratory failure of pigs. Am Rev Respir Dis 135:93–99, 1987
21. Lamy M, Deby-Dupont G, Pincemail J, Braun M, Duchateau J, Deby C, Van Erck J, Bodson L, Damas P, Franchimont P: Biochemical pathways of acute lung injury. Bull Eur Physiopath Respir 21:221–229, 1985
22. Matthay MA, Eschenbacher WC, Goetze EF: Elevated concentrations of leukotriene D4 in pulmonary edema fluid of patients with the adult respiratory distress syndrome. J Clin Immunol 4:479–483, 1984
23. Ralph DD, Robertson HT, Weaver LJ, Hlastala MP, Carrico CJ, Hudson LD: Distribution of ventilation and perfusion during positive end-expiratory pressure in the adult respiratory distress syndrome. Am Rev Respir Dis 131:54–60, 1985
24. Prewitt RM, Wook LDH: Effect of sodium nitroprusside on cardiovascular function and pulmonary shunt in canine oleic acid pulmonary edema. ANESTHESIOLOGY 55:537–541, 1981
25. Colley PS, Cheney FW, Hlastala MP: Ventilation perfusion and gas exchange effects of sodium nitroprusside in dogs with normal and edematous lungs. ANESTHESIOLOGY 50:489–495, 1979
26. Lemaire F, Jardin F, Harari A, Teisseire B, Laurent D, Rapin M: Assessment of gas exchange during veno-arterial bypass using the membrane lung, Artificial Lungs for Acute Respiratory Failure. Edited by Zapol WM, Qvist J. New York, Academic Press, 1976, pp 421–433.
27. Sandoval J, Long GR, Skoog C, Wood LDH, Oppenheimer L: Independent influence of blood flow rate and mixed venous P_{O_2} on shunt fraction. J Appl Physiol 55:1128–1133, 1983
28. Benumof JL: One-lung ventilation and hypoxic pulmonary vasoconstriction. Anesth Analg 64:821–833, 1985
29. Huet Y, Brun-Buisson C, Lemaire F, Teisseire B, Lhoste F, Rapin M: Cardiopulmonary effects of ketanserin infusion in human pulmonary embolism. Am Rev Respir Dis 1935:114–117, 1987

Anesthesiology
68:157–163, 1988

The Influence of Fentanyl and Tracheal Intubation on the Hemodynamic Effects of Anesthesia Induction with Propofol/N_2O in Humans

HUGO VAN AKEN, M.D.,* ECKHARD MEINSHAUSEN, M.D.,†
THOMAS PRIEN, M.D.,† THOMAS BRÜSSEL, M.D.,† ACHIM HEINECKE, PH.D.,‡ PETER LAWIN, M.D.*

Previous studies on the hemodynamic effects of anesthesia induction with propofol, a phenol derivative (2,6-diisopropylphenol) have reported a significant decrease of both systolic and diastolic arterial pressure in heavily sedated patients with coronary artery disease[1] and in patients with aortic and mitral valve disorders.[2] In these studies, the original cremophor formulation of propofol had been used. As cremophor-containing anesthetics are associated with a significant frequency of anaphylactoid reactions, propofol has been reformulated as an aqueous emulsion (1% propofol, 10% soya bean oil, 2.25 glycerol, and 1.2% egg phosphatide).[3] Using the new formulation for induction of anesthesia, significant decreases in arterial pressure in combination with a slight fall in cardiac output have been observed in healthy patients breathing air[4] or 100% oxygen.[5]

Propofol, by virtue of its short duration of action and rapid elimination phase,[6] would appear to have an ideal pharmacologic profile for use in short surgical procedures. However, the anesthetic depth achieved with hypnotic agents may often be insufficient for surgery, and additional agents with analgesic properties, such as nitrous oxide or narcotics, are required. Therefore, the hemodynamic effects of anesthesia induction with propofol (the new formulation), alone and in combination with fetanyl, were studied in patients breathing 30% oxygen in nitrous oxide. A second purpose of this study was to evaluate the hemodynamic responses arising

* Professor of Anesthesia.
† Resident in Anesthesia.
‡ Biomathematician.

Received from the Klinik für Anästhesiologie und operative Intensivmedizin der Westfälischen Wilhelms-Universität Münster, Albert-Schweitzer-Str. 33, 4400 Münster, West Germany; and the Institut für Medizinische Informatik und Biomathematik der Westfälischen Wilhelms-Universität Münster, Domagkstr. 9, 4400 Münster, West Germany. Accepted for publication August 24, 1987.

Address reprint requests to Dr. Van Aken: Chairman of the Department of Anesthesia, Katholieke Universiteit Leuven, Herestraat 49, 3000 Leuven, Belgium.

Key words: Anesthetics, gases: nitrous oxide. Anesthetics, intravenous: fentanyl; propofol. Induction, anesthesia: cardiovascular effects. Intubation, endotracheal.

TABLE 1. Patient Characteristics, Data are Mean ± SEM (n = 10 in Each Group)

	Group A (Propofol)	Group B (Propofol, Fentanyl)	Group C (Propofol, Intubation)	Group D (Propofol, Fentanyl, Intubation)
Age (years)	59.1 ± 3.0	57.5 ± 2.8	53.5 ± 1.9	60.8 ± 2.9
Height (cm)	172.1 ± 2.9	175.5 ± 1.7	171.9 ± 2.4	168.60 ± 2.1
Weight (kg)	73.8 ± 4.0	75.8 ± 3.7	70.2 ± 2.4	64.7 ± 4.1
BSA (m^2)	1.86 ± 0.06	1.91 ± 0.04	1.82 ± 0.04	1.73 ± 0.05

from tracheal intubation during propofol/nitrous oxide and propofol/fentanyl/nitrous oxide anesthesia.

MATERIALS AND METHODS

Forty ASA P.S. I–II patients scheduled for major abdominal or vascular surgery were studied. The study was approved by the Ethical Committee and informed consent was obtained from all patients. Patients did not qualify for this study if they had a history of allergy, were obese (>120% of ideal body weight), or had symptoms or signs of hepatic, renal, hematologic, or metabolic disease. All patients were premedicated with 1 mg lormetazepam (benzodiazepine) p.o. 2 h before anesthesia. On arrival in the operating room, an electrocardiograph was attached and a modified V5 lead continuously displayed. Cannulae were inserted into a peripheral vein and a radial artery after local anesthesia. A continuous intravenous infusion of lactated Ringer's solution was maintained at a rate of 10 ml/kg per hour for the study period. A balloon-tipped flow-directed thermodilution catheter was inserted into the pulmonary artery *via* the internal jugular vein. All pressures were recorded using pressure-transducers (Gould P23ID, Gould Inc., Oxnard, CA) and continuously displayed on a four-channel chart recorder. Cardiac output (Cardiac output computer 9510, American Edwards Laboratories, Irvine, CA) was measured by the thermodilution technique using iced glucose solution. For each determination of cardiac output two measurements were obtained and averaged. The following baseline data were collected 20 min after insertion of all catheters: heart rate (HR); systolic (SAP), diastolic (DAP), and mean (MAP) arterial pressure; pulmonary artery systolic (PAS), diastolic (PAD), and mean (PAP) arterial pressure; pulmonary capillary wedge pressure (PCWP); central venous pressure (CVP); cardiac output (CO); arterial *p*H (*p*Ha), P_{O_2} (pa_{O_2}), and p_{CO_2} (pa_{CO_2}). Systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), and stroke volume (SV) were calculated using standard formulae.[7]

The patients were randomly assigned to four study groups. In group A, propofol (approximately 2.5 mg/kg) was injected intravenously over 60 s. With disappearance of the eyelash reflex, the patients were manually ventilated with 30% oxygen in nitrous oxide *via* a tight-fitting face mask, carefully avoiding raised airway pressures. At 1, 3, 5, 8, and 10 min after the start of propofol injection, the same hemodynamic variables were again measured (arterial blood gases were measured 5 and 10 min later). In group B, the same sequence was used except that the dose of propofol was immediately preceded by intravenous injection of 3 μg/kg fentanyl. Patients in groups C and D were treated the same as in groups A and B, respectively; but, in addition, had their tracheas intubated: 100 μg/kg vecuronium were given intravenously after manual ventilation had been established. Four minutes after the start of propofol injection, direct laryngoscopy and placement of a naso-gastric and oro-tracheal tube were performed with 45 s, in all cases by the same person. The time points for data collection in groups C and D were the same as in groups A and B.

Data presented are mean ± SEM. For statistical comparisons of means within a group, the Friedman-test was used. For statistical comparisons of means between group A and B, and group C and D, the Mann-Whitney-Wilcoxon test was used. Statistically significant differences were accepted at $P \leq 0.05$.[8]

RESULTS

The demographic data of the patients are listed in table 1. There were no significant differences between groups with regard to age, weight, height, and body surface area (BSA). Table 2 summarizes the type of surgery, preexisting cardiovascular diseases, and chronic medication. There were no significant differences between groups. The doses of propofol required to abolish lid reflex in groups A, B, C, and D were 2.4 ± 0.1, 2.4 ± 0.2, 2.3 ± 0.1, and 2.3 ± 0.1 mg/kg, respectively (NS).

The hemodynamic changes following induction of anesthesia are listed in tables 3 and 4. There were no statistically significant differences in baseline values among the four groups. Blood gas data are summarized in table 5. There were no statistically significant differences between groups at the three time-points with regard to pa_{O_2} and pa_{CO_2}.

Induction of Anesthesia Without Endotracheal Intubation (Groups A and B) (table 3). In both groups, SV decreased immediately following injection of the drugs and re-

TABLE 2. Cardiovascular Diseases, Chronic Medication, and Type of Surgery

	Group A (n = 10)	Group B (n = 10)	Group C (n = 10)	Group D (n = 10)
Cardiovascular disease				
Ischemic heart disease*	6	4	6	5
Systemic hypertension†	2	3	1	1
Chronic medication				
Antihypertensives	1	1	0	0
Antiarrhythmics	2	0	3	1
Diuretics	2	0	1	1
Beta-adrenergic-blocking agents	1	0	0	0
Type of surgery				
A) *Vascular*				
Aorta bifemoral bypass graft	4	3	4	4
Femoro popliteal bypass graft	2	2	1	2
B) *Abdominal*				
Gastrectomy	2	1	2	1
Whipple	2	3	2	2
Miscellaneous	0	1	1	1

* As evidenced by preoperative 12-lead ECG.
† Systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 95 mmHg

mained at this level for the rest of the observation period. This decrease in SV was of the order of 15–20 ml/beat. There was no change of HR in group A. The combination of propofol and fentanyl, however, induced a significant decrease in HR beginning 3 min after injection of the drugs and lasting for the rest of the observation period. In both groups, SAP, MAP, DAP, and CO fell immediately following injection ($P \geq 0.05$). These decreases in arterial pressures and CO were statistically significant 3 min after start of the propofol

TABLE 3. Hemodynamic Data (Mean ± SEM) (n = 10 in Each Group) during Induction of Anesthesia in Group A (Propofol 2.4 ± 0.1 mg/kg) and Group B (Fentanyl 3 μg/kg, Propofol 2.4 ± 0.2 mg/kg)

	Awake	1	3	5	8	10
Group A						
HR (beats · min^{-1})	87 (6)	89 (4)	87 (6)	85 (5)	83 (5)	81 (5)
SAP (mmHg)	166 (9)	150 (10)	124 (7)*	124 (7)*	112 (7)*	115 (7)*
DAP (mmHg)	70 (4)	65 (4)	60 (5)*	60 (5)*	57 (5)*	56 (5)*
MAP (mmHg)	102 (5)	91 (6)	81 (5)*	81 (6)*	75 (5)*	78 (6)*
PAS (mmHg)	27.5 (2.7)	23.6 (2.9)	23.2 (2.3)	25.1 (2.5)	24.3 (2.3)	26.0 (2.6)
PAD (mmHg)	5.8 (1.2)	6.6 (1.5)	8.1 (1.2)	7.8 (1.0)	8.1 (0.8)	6.1 (0.9)
PAP (mmHg)	14.9 (1.5)	15.1 (1.7)	14.9 (1.5)	14.7 (1.5)	14.7 (1.4)	15.5 (1.4)
CVP (mmHg)	2.3 (0.6)	2.9 (0.7)	5.1 (1.4)	5.8 (1.3)*	4.9 (1.2)	5.6 (1.0)*
PCWP (mmHg)	3.1 (0.5)	4.5 (0.9)	4.0 (0.8)	4.5 (0.8)	3.9 (0.8)	3.5 (0.6)
CO (l · min^{-1})	7.5 (0.7)	6.1 (0.5)	6.2 (0.5)	5.8 (0.5)*	5.6 (0.4)*	6.2 (0.7)
SV (ml · beat^{-1})	88.1 (8.0)	69.1 (6.1)	73.1 (7.0)	68.8 (5.2)*	68.7 (5.5)*	78.4 (8.5)
SVR (dyn · sec · min^{-5})	1135 (106)	1240 (129)	1053 (134)	1121 (139)	1070 (131)	1015 (121)
PVR (dyn · sec · min^{-5})	137 (24)	151 (32)	148 (20)	146 (16)	162 (16)	173 (26)
Group B						
HR (beats · min^{-1})	80 (3)	79 (3)	68 (1)*†	65 (1)*†	63 (2)*†	62 (2)*†
SAP (mmHg)	160 (5)	135 (8)	98 (6)*†	87 (6)*†	84 (6)*†	84 (6)*†
DAP (mmHg)	71 (3)	62 (4)	48 (3)*	43 (2)*†	42 (3)*†	43 (3)*†
MAP (mmHg)	102 (5)	85 (6)	63 (4)*†	58 (4)*†	56 (4)*†	57 (4)*†
PAS (mmHg)	23.8 (2.1)	21.8 (1.7)	21.7 (1.5)	21.5 (1.9)	23.1 (1.9)	23.9 (2.2)
PAD (mmHg)	6.4 (1.1)	8.6 (1.1)	7.6 (1.0)	8.4 (1.0)	8.1 (1.2)	8.2 (1.1)
PAP (mmHg)	14.1 (1.6)	14.7 (1.4)	14.1 (1.3)	14.1 (1.2)	14.5 (1.3)	14.6 (1.4)
CVP (mmHg)	2.9 (0.5)	4.2 (0.5)	5.1 (0.7)*	4.2 (0.8)	5.4 (0.8)*	6.2 (0.9)*†
PCWP (mmHg)	3.6 (0.7)	5.6 (1.1)	5.3 (0.88)	6.2 (0.8)*	6.3 (1.0)*	6.2 (0.9)*
CO (l · min^{-1})	7.9 (0.7)	6.3 (0.6)	5.4 (0.5)*†	5.4 (0.5)*	5.1 (0.5)*	5.1 (0.5)*
SV (ml · beat^{-1})	99.4 (7.6)	79.7 (7.4)*	79.4 (7.5)*	81.9 (7.8)*	81.9 (8.3)*	83.8 (8.9)*
SVR (dyn · sec · min^{-5})	1078 (107)	1058 (150)	918 (74)	833 (54)*	819 (59)*	825 (56)*
PVR (dyn · sec · min^{-5})	109 (12)	128 (15)	142 (18)	127 (15)	133 (12)	140 (16)

Comparison to awake values within the group *$P \leq 0.05$. Comparison between the groups †$P \leq 0.05$.

TABLE 4. Hemodynamic Data (Mean ± SEM) (n = 10 in Each Group) during Induction of Anesthesia in Group C (Propofol 2.3 ± 0.1 mg/kg, Vecuronium 100 μg/kg) and Group D (Propofol 2.3 ± 0.1 mg/kg, Fentanyl 3 μg/kg, Vecuronium 100 μg/kg). Endotracheal Intubation was Performed at the 4th minute

	Awake	1	3	5	8	10
Group C						
HR (beats · min^{-1})	83 (4)	84 (4)	78 (4)	90 (5)	83 (3)	80 (4)
SAP (mmHg)	157 (6)	142 (8)	110 (7)*	173 (9)*	136 (6)	136 (7)
DAP (mmHg)	67 (2)	59 (4)	55 (3)*	84 (4)*	63 (3)	66 (4)
MAP (mmHg)	98 (4)	85 (5)	75 (5)*	115 (5)*	91 (4)	92 (5)
PAS (mmHg)	22.1 (1.9)	19.5 (1.5)	18.2 (1.2)	24.7 (1.8)	22.5 (1.8)	23.1 (1.9)
PAD (mmHg)	6.2 (1.1)	6.6 (0.8)	5.8 (0.7)	9.3 (1.3)*	7.7 (1.2)	7.3 (0.7)
PAP (mmHg)	12.0 (1.2)	11.9 (0.8)	10.8 (0.7)	15.4 (1.2)*	13.3 (1.2)	13.8 (0.9)
CPV (mmHg)	2.1 (0.6)	3.5 (0.8)	4.3 (1.0)*	4.1 (0.9)*	3.8 (0.9)*	3.8 (0.9)*
PCWP (mmHg)	3.9 (0.6)	3.7 (0.7)	3.8 (0.6)	5.3 (0.9)	4.0 (0.9)	4.7 (0.7)
CO (l · min^{-1})	7.0 (0.4)	5.8 (0.5)	6.2 (0.5)	6.5 (0.5)	7.1 (0.6)	6.2 (0.4)
SV (ml · beat^{-1})	84.7 (4.5)	70.5 (5.9)	75.1 (7.0)	72.9 (4.7)	86.7 (6.5)	78.1 (4.4)
SVR (dyn · sec · min^{-5})	1123 (63)	1180 (113)	957 (95)	1422 (97)	1031 (83)	1180 (98)
PVR (dyn · sec · min^{-5})	94 (12)	116 (14)	92 (7)	128 (10)*	110 (10)	122 (13)
Group D						
HR (beats · min^{-1})	83 (5)	83 (4)	72 (6)*	90 (6)	76 (6)	74 (7)
SAP (mmHg)	149 (10)	126 (7)*	92 (7)*	142 (11)†	118 (11)*	107 (10)*†
DAP (mmHg)	66 (4)	57 (3)	45 (4)*†	72 (5)	58 (5)	53 (5)*†
MAP (mmHg)	95 (5)	76 (4)*	61 (5)*	97 (7)	80 (7)*	71 (7)*†
PAS (mmHg)	21.8 (1.4)	20.1 (1.6)	17.8 (1.3)	24.7 (2.5)	22.5 (1.6)	20.9 (1.3)
PAD (mmHg)	4.0 (0.3)	5.8 (1.3)	5.2 (0.5)	8.9 (1.8)*	6.0 (1.3)*	5.7 (1.1)*
PAP (mmHg)	10.8 (0.9)	11.4 (1.2)	10.4 (1.0)	16.1 (1.9)*	12.6 (1.2)	12.2 (1.2)
CVP (mmHg)	2.4 (0.5)	4.1 (0.8)	3.4 (0.8)	5.5 (0.8)*	5.2 (0.6)*	4.9 (0.9)*
PCWP (mmHg)	2.0 (0.4)	3.1 (0.8)	3.2 (0.8)	4.5 (1.1)	3.4 (0.8)	3.2 (0.7)
CO (l · min^{-1})	6.6 (0.5)	4.6 (0.2)*†	4.8 (0.4)*†	6.2 (0.5)	4.7 (0.3)*†	5.1 (0.4)*
SV (ml · beat^{-1})	80.2 (5.1)	56.9 (3.0)*	68.1 (5.5)*	71.3 (7.1)*	64.2 (4.6)*†	71.2 (6.0)*
SVR (dyn · sec · min^{-5})	1172 (101)	1260 (60)	1026 (129)	1277 (158)	1327 (151)	1083 (109)
PVR (dyn · sec · min^{-5})	111 (11)	148 (16)	127 (14)	168 (30)*	159 (16)*	151 (18)

Comparison to awake values within the group *$P \leq 0.05$. Comparison between the groups †$P \leq 0.05$.

injection and thereafter; they were more pronounced in group B than in group A ($P \leq 0.05$). PAP did not change significantly in either group. SVR did not change in group A, but decreased in group B ($P \leq 0.05$). CVP and PCWP increased in both groups. This trend was more pronounced in group B, in which significant increases of CVP and PCWP were observed; whereas, in group A, this trend was only significant for CVP.

Induction of Anesthesia Followed by Endotracheal Intubation (Groups C and D) (table 4). Up to the time of laryngoscopy, the hemodynamic changes in group C are similar to group A, and those of group D similar to group B: SV decreased; HR remained unchanged with propofol alone, while the combination with fentanyl induced a significant decrease in HR; SAP, MAP, DAP, and CO decreased (these changes were more pronounced with the combination of propofol and fentanyl); PAP remained unchanged; and CVP and PCWP increased somewhat, though not significantly.

Immediately following laryngoscopy (time-point 5 min), HR was increased in both groups, but not significantly above baseline values. SAP, MAP, and DAP returned to baseline values in group D, while they were

TABLE 5. Arterial Blood Gases and *p*H Before and Following Induction of Anaesthesia. Data are Mean ± SEM (n = 10 in Each Group)

	Awake			Minutes after Induction: 5			10		
	*p*H	P_{O_2}	P_{CO_2}	*p*H	P_{O_2}	P_{CO_2}	*p*H	P_{O_2}	P_{CO_2}
Group A	7.4 (0.01)	83 (6)	38 (1)	7.38 (0.01)	162 (11)	40 (2)	7.36 (0.02)	153 (11)	41 (2)
Group B	7.4 (0.01)	78 (3)	37 (1)	7.38 (0.01)	140 (13)	38 (2)	7.4 (0.01)	138 (11)	37 (2)
Group C	7.4 (0.01)	83 (5)	38 (3)	7.38 (0.01)	130 (14)	39 (2)	7.39 (0.02)	131 (13)	38 (3)
Group D	7.4 (0.34)	77 (3)	37 (4)	7.37 (0.2)	135 (13)	37 (3)	7.37 (0.04)	141 (9)	37 (3)

significantly higher than at baseline in group C. In both groups, PAP was significantly higher than at baseline, immediately following endotracheal intubation. For CVP and PCWP, no major effects of endotracheal intubation were observed, with the exception of a slight increase in CVP above baseline values in group D ($P \leq 0.05$). Stroke volume was unaffected and remained reduced in both groups. Cardiac output returned towards baseline values in both groups, still being reduced by approximately 0.5 l/min. Three and five minutes following laryngoscopy (time-points 8 min and 10 min), the hemodynamic pattern of group C was unchanged from the baseline pattern, except that CVP remained at its slightly elevated level ($P \leq 0.05$). In group D, however, SAP, MAP, DAP, and CO decreased below baseline values again ($P \leq 0.05$). These decreases in arterial pressures and CO were also significant when compared to group C at time-point 10 min and 8 min, respectively. SV remained decreased in this group ($P \leq 0.05$). PAP returned towards baseline values, while CVP and PCWP remained at their slightly elevated levels.

Discussion

We investigated the effect of the combination of propofol and N_2O in this study, because N_2O is often administered as a supplementary anesthetic immediately following induction with intravenous agents. To achieve even better analgesia, the additional use of opiates may be necessary. The effect of this combination (propofol/N_2O/fentanyl), therefore, was also studied.

Baseline arterial pressures, heart rate, and cardiac output indicate that, despite premedication with 1 mg lormetazepam p.o. 2 h before arrival in the induction area, at least some of the patients were anxious prior to induction of anesthesia. Thus, the observed changes of hemodynamic parameters following induction of anesthesia may, in part, be interpreted as a "normalization." However, changes in blood pressure, cardiac output, and stroke volume were more pronounced than those accompanying deep sleep in normal volunteers.[9] Previous studies on the effects of anesthesia induction with the aqueous emulsion of propofol have reported conflicting data. These can, to some extent, be attributed to different protocols. In patients breathing air, Fahmy *et al.* found a decrease in MAP due to a decrease in SVR, while CO did not change.[4] In contrast, in patients breathing 66% nitrous oxide in oxygen while receiving a constant intravenous infusion of 54 or 108 μg/kg/min propofol, Prys-Roberts *et al.*,[10] as well as Coates *et al.*,[11] reported a decrease in MAP that could be attributed to a decrease in SV and CO. Similarly, in the present study, we observed a significant decrease in MAP that was predominantly due to a reduced SV and CO, while SVR showed only minor changes. Thus, the difference in the hemodynamic patterns of propofol/N_2O and propofol/oxygen or air, are likely the result of the cardiovascular actions of nitrous oxide in combination with propofol.

Eisele demonstrated that N_2O produces a 15–20% reduction in cardiac output as a result of both a decrease in HR and contractility, and a 20% increase in SVR.[12] Animal studies suggest that a rise in SVR is due to an increased activity of the sympathetic nervous system.[13] Apart from the effects of nitrous oxide, a negative inotropic action of propofol must be considered. In a canine model, it has been shown recently that propofol exhibits negative inotropic effects. A bolus injection of 2.5 mg/kg propofol caused a significant decrease of myocardial mesh tension,[14] whereas no decrease was observed after injection of 0.3 mg/kg etomidate.§ Finally, the dose-response relationship of cardiovascular depression has to be considered. Previous reports claiming cardiovascular stability of the cremophor formulation were based on smaller induction doses[15–17] than the induction dose required with the aqueous emulsion of propofol,[18] which is generally accepted to be 2.5 mg/kg.[4,19–21] Briggs *et al.* mentioned that the cardiovascular depression of the cremophor formulation was dose related, being more pronounced above 2 mg/kg.[17]

The present study confirms the absence of an increase in heart rate with propofol.[1,5,10,18–21] The change in HR in relation to the fall in arterial pressure caused by intravenous agents is variable.[22] With falling blood pressure, a reflex increase in HR would be expected.

Prys-Roberts has reported that propofol resets the baroreflexes to allow slower heart rates at lower arterial pressures.¶

The additional administration of fentanyl (group B and D) results in a further significant decrease in arterial pressure and cardiac output. A significant decrease in HR also occurred. Small decreases in HR and, possi-

§ Brüssel T, Vigfusson G, Lunkenheimer P, Theissen J, Lawin P. Influence of diprivan and etomidate on cardiodynamic parameters in the dog (abstract). VII European Congress of Anaesthesiology Abstracts II, Beiträge zur Anästhesiologie und Intensivmedizin Band 17. Edited by Bergman H, Kramer H, Steinbereithner K. Wien-München-Bern, Wilhelm Maudrich Verlag, 1986, p 142

¶ Prys-Roberts C. Haemodynamic effects of "Diprivan" infusion anaesthesia: Comparison with other intravenous and volatile anaesthetics (abstract). VII European Congress of Anaesthesiology Abstracts III, Beiträge zur Anästhesiologie und Intensivmedizin Band 18. Edited by Bergman H, Kramer H, Steinbereithner K. Wien-München-Bern, Wilhelm Maudrich Verlag, 1986, p 296

bly, blood pressure do occur after fentanyl,[23,24] especially in patients who have not received atropine.[25] In addition, a negative inotropic action of propofol might be expected to be enhanced by supplementary fentanyl, in a manner similar to the additive negative inotropic effect of a combination of diazepam and fentanyl.[26] Our data are consistent with observations made following the cremophor formulation of propofol, where the greatest decreases in blood pressure occurred when the drug was given to patients who concurrently received opiates.[27]

A modest hypertensive reaction immediately following tracheal intubation occurred when propofol alone was used with nitrous oxide (group C), and this was attenuated with the combination of propofol and 3 μg/kg fentanyl (group D). This finding is consistent with previous investigations of anesthetics combined with fentanyl to blunt circulatory responses to tracheal intubation.[28] However, the combination of fentanyl and propofol produces an important hemodynamic depression before, and 3 and 5 min after, tracheal intubation.

The other hemodynamic parameters measured in this study (PAP, PCWP, CVP, SVR) show only minor and clinically insignificant changes. The increases in CVP and PCWP can, in part, be attributed to increased intrathoracic pressures. PAP increased transiently following intubation. Therefore, propofol, whether administered alone or in combination with 3 μg/kg fentanyl, did not completely suppress the hypertensive response of the pulmonary vasculature following endotracheal intubation. Of clinical importance is the observation that the combination of propofol and fentanyl—even in the presence of nitrous oxide, which increases SVR—results in a reduction of SVR. Thus, the pronounced reduction in blood pressure with propofol and fentanyl must be a result of: 1) a decrease in CO due to decreased HR and SV, and 2) vasodilation.

No direct comparison between propofol and other intravenous induction agents has been made in this study. Previous studies, comparing anesthesia induction with 2.5 mg propofol and 4 and 5 mg/kg thiopental, have reported a more pronounced cardiovascular depression with propofol.[5,29]

In conclusion, propofol in its new oil-in-water emulsion, with 70% nitrous oxide, is a cardiovascular depressant in patients without significant cardiovascular disease. Anesthesia induction with 2.5 mg/kg propofol, in combination with 70% nitrous oxide, causes a fall in blood pressure, cardiac output, and stroke volume, suggesting a negative inotropic action. The cardiovascular depressant effect of propofol-nitrous oxide is increased when 3 μg/kg fentanyl is added. Care should be taken in patients with cardiovascular diseases, as the cardiovascular depression may be far less predictable and, potentially, more serious.

References

1. Al-Khudhairi D, Gordon G, Morgan M, Whitwam JG: Acute cardiovascular changes following disoprofol. Effects in heavily sedated patients with coronary artery disease. Anaesthesia 37:1007–1010, 1982
2. Aun C, Major E: The cardiorespiratory effect of ICI 35868 in patients with valvular heart disease. Anaesthesia 39:1096–1100, 1984
3. Glen JB, Hunter SC: Pharmacology of an emulsion formulation of ICI 35868. Br J Anaesth 56:617–626, 1984
4. Fahmy NR, Alkhouli HM, Sunder M, Smith D, Kelley MM: Diprivan: A new intravenous induction agent. A comparison with thiopental (abstract). ANESTHESIOLOGY 63:A363, 1985
5. Grounds RM, Twigley AJ, Carli F, Whitwam JG, Morgan M: The haemodynamic effects of intravenous induction. Comparison of the effects of thiopentone and propofol. Anaesthesia 40:735–740, 1985
6. Adam HK, Briggs LP, Bahar M, Douglas EJ, Dundee JW: Pharmacokinetic evaluation of ICI 35868 in man. Br J Anaesth 55:97–102, 1983
7. Kappagoda CT, Linden RJ: The use of SI units in cardiovascular studies. Cardiovasc Res 10:141–148, 1976
8. Miller RG Jr: Simultaneous Statistical Influence. New York-Heidelberg-Berlin, Springer Verlag, 1981
9. Khatri JM, Freis ED: Hemodynamic changes during sleep. J Appl Physiol 22:867–873, 1967
10. Prys-Roberts C, Davies JR, Calverley RK, Goodman NW: Haemodynamic effects of infusions of diisopropyl phenol (ICI 35868) during nitrous oxide anaesthesia in man. Br J Anaesth 55:105–111, 1983
11. Coates DP, Prys-Roberts C, Spelina KR, Monk CR, Norley I: Propofol (Diprivan) by intravenous infusion with nitrous oxide: Dose requirements and haemodynamic effects. Postgrad Med J 61 (Suppl) 3:76–79, 1985
12. Eisele JH, Smith NT: Cardiovascular effects of 40 percent nitrous oxide in man. Anesth Analg 51:956–963, 1972
13. Fukunaga AF, Epstein RM: Sympathetic excitation during nitrous oxide-halothane anesthesia in the cat. ANESTHESIOLOGY 39:23–36, 1973
14. Lunkenheimer PP, Lunkenheimer A, Torrent-Guasp F: Kardiodynamik: Wege zur strukturgerechten Analyse der Myokardfunktion. Erlangen, Perimed Fachbuch-Verlagsgesellschaft mbH, 1985, pp 106–129
15. Kay B, Rolly G: ICI 35868, a new intravenous induction agent. Acta Anaesthesiol Belg 28:303–316, 1977
16. Fragen RJ, Hanssen EHJH, Denissen PAF, Booij LHDJ, Crul JF: Disoprofol (ICI 35868) for total intravenous anaesthesia. Acta Anaesthesiol Scand 27:113–116, 1983
17. Briggs LP, Clarke RSJ, Dundee JW, Moore J, Bahar M, Wright PJ: Use of Di-isopropyl phenol as a main agent for short procedures. Br J Anaesth 53:1197–1202, 1981
18. Cummings GC, Dixon J, Kay NH, Windsor JPW, Major E, Morgan M, Sear JW, Spence AA, Stephenson DK: Dose requirements of ICI 35868 (Propofol, 'Diprivan') in a new formulation for induction of anaesthesia. Anaesthesia 39:1168–1171, 1984
19. Rolly G, Versichelen L: Comparison of propofol and thiopentone for induction of anaesthesia in premedicated patients. Anaesthesia 40:945–948, 1985
20. Mouton SM, Bullington J, Davis L, Fisher K, Ramsey S, Wood M:

A comparison of diprivan and thiopental for the induction of anesthesia (abstract). ANESTHESIOLOGY 63:A364, 1985
21. Youngberg JA, Grogono AW, Sehon CK, White J, Texidor M: Comparative evaluation of Diprivan, Thiopental and Thiamylal for induction of anesthesia (abstract). ANESTHESIOLOGY 63:A365, 1985
22. Reves JG, Gelman S: Cardiovascular effects of intravenous anesthetic drugs, Effects of Anesthesia. Edited by Covino BJ, Fozzard HA, Rehder K, Strichartz G. Baltimore, Williams & Wilkins Co., 1985, 179–193
23. Tammisto T, Takki S, Toikka P: A comparison of the circulatory effects in man of the analgesics fentanyl, pentazocine and pethidine. Br J Anaesth 42:317–324, 1970
24. Graves CL, Downs NH, Browne AB: Cardiovascular effects of minimal analgesic quantities of Innovar, fentanyl, and droperidol in man. Anesth Analg 54:15–25, 1975
25. Laubie M, Schmitt H, Drauillat M: Central sites and mechanisms of the hypotensive and bradycardic effects of the narcotic analgesic fentanyl. Naunyn Schmiedebergs Arch Pharmacol 256:255–261, 1977
26. Reves JG, Kissin J, Fournier SE, Smith LR: Additive negative inotropic effect of a combination of diazepam and fentanyl. Anesth Analg 63:97–100, 1984
27. Briggs LP, Bahar M, Beers HTB, Clarke RSJ, Dundee JW, Wright PJ, McAuley DM, O'Neill MP: Effect of preanaesthetic medication on anaesthesia with ICI 35868. Br J Anaesth 54:303–306, 1982
28. Martin DE, Rosenberg H, Aukburg SJ, Bartkowski RR, Edwards MM Jr, Greenhow DE, Klineberg PL: Low dose fentanyl blunts circulatory responses to tracheal intubation. Anesth Analg 61:680–684, 1982
29. Fahy LT, van Mourik GA, Utting JE: A comparison of the induction characteristics of thiopentone and propofol (2,6-di-isopropyl phenol). Anaesthesia 40:939–944, 1985