14. Nakao K, Miyata M: The influence of phentolamine, an adrenergic blocking agent, on insulin secretion during surgery. Eur J Clin Invest 7:41–45, 1977
15. Hamaji M, Nakao K, Kiso K: Pancreatic glucagon and insulin response during surgery. Horm Metab Res 11:488–489, 1979
16. Watson BG: Blood glucose level in children during surgery. Br J Anaesth 44:712–715, 1972
17. Payne K, Ireland P: Plasma glucose levels in the peri-operative period in children. Anaesthesia 39:868–872, 1984
18. Oyama T, Takiguchi M, Kudo T: Metabolic effects of anaesthesia: Effect of thiopentone-nitrous oxide anaesthesia on human growth hormone and insulin levels in plasma. Can Anaesth Soc J 18:442–453, 1971
19. Cerasi E, Luft R, Efendic S: Antagonism between glucose and epinephrine regarding insulin secretion. A dose-response study in man. Acta Med Scand 190:411–417, 1971
20. Walsh ES, Traynor C, Paterson JL, Hall GM: Effect of different intraoperative fluid regimens on circulating metabolites and insulin during abdominal surgery. Br J Anaesth 55:135–140, 1983
21. Baxter JD, Forsham PM: Tissue effects of glucocorticoids. Am J Med 53:573–589, 1972
22. Oyama T, Takazawa T: Effect of methoxyflurane anaesthesia and surgery on human growth hormone and insulin levels in plasma. Can Anaesth Soc J 17:347–358, 1970
23. Oyama T, Takazawa T: Effects of halothane anaesthesia and surgery on human growth hormone and insulin levels in plasma. Br J Anaesth 43:573–580, 1971
24. Oyama T, Matsuki A, Kudo M: Effects of enflurane (Ethrane) anaesthesia and surgery on carbohydrate and fat metabolism in man. Anaesthesia 27:179–184, 1972
25. Lacoumenta S, Paterson JL, Burrin J, Causon RC, Brown MJ, Hall GM: Effects of two differing halothane concentrations on the metabolic and endocrine responses to surgery. Br J Anaesth 58:844–850, 1986
26. Faber OK, Kehlet H, Madsbad S, Binder C: Kinetics of human C-peptide in man. Diabetes 27 (suppl 1):207–209, 1978
27. Johnston DG, Alberti KGMM, Faber OK, Binder C, Wright R: Hyperinsulinism of hepatic cirrhosis: Diminished degradation or hypersecretion? Lancet 1:10–13, 1977
28. Madsbad S, Kehlet H, Hilsted J, Tronier B: Discrepancy between plasma C-peptide and insulin response to oral and intravenous glucose. Diabetes 32:436–438, 1983
29. Miyata M, Yamamoto T, Nakao K: Suppression of glucagon secretion during surgery. Horm Metab Res 8:239–240, 1976
30. Persson B, Feychting H, Josephson S, Larsson A, Settergren G, Tordai P: Rehydration using solution with and without glucose before emergency abdominal surgery in children. Acta Anaesthesiol Scand 27:35–38, 1983
31. Bhathena SJ, Voyles NR, Joshi B, Engel WK, Smith SS, Recant L: Acute changes in human erythrocyte insulin receptors. Horm Metab Res 13:179–180, 1981

Anesthesiology
68:152–157, 1988

Comparison of Ketanserin and Sodium Nitroprusside in Patients with Severe ARDS

PETER RADERMACHER, M.D.,* YANN HUET, M.D.,† FRÉDÉRIC PLUSKWA, M.D.,‡ ROBERT HERIGAULT,§ HERVÉ MAL, M.D.,‡ BERNARD TEISSEIRE, PH.D,¶ FRANÇOIS LEMAIRE, M.D.**

Pulmonary artery hypertension (PAH) due to an increased pulmonary vascular resistance is a common event in adult respiratory distress syndrome (ARDS).[1] PAH increases right ventricular afterload, and may lead to right ventricular dysfunction.[2] Moreover, PAH enhances the accumulation of extravascular lung water[3] by increasing the net microvascular filtration pressure.[4] Because of these potentially deleterious effects, therapy with vasodilators, especially with sodium nitroprusside (SNP), has been attempted both in animal models[5] and in patients with ARDS.[6,7] The clinical use of vasodilators has been limited, however, because pulmonary vasodilation usually impairs gas exchange.

Serotonin, which is released by activated platelets, is a putative mediator of PAH associated with ARDS,[8] because pulmonary platelet entrapment can occur in acute respiratory failure.[9] Ketanserin, a specific receptor antagonist of serotonin,[10] is able to moderately decrease pulmonary artery pressure (PAP) when infused in patients with ARDS.[11,12] Surprisingly, the hemodynamic changes occurred without the expected detrimental effects on gas exchange. To further explain the hemodynamic and gas exchange alterations induced by ketanserin, we used pulmonary artery catheterization and the multiple inert gas elimination technique to define gas

* Research Fellow, Department of Medical Intensive Care.
† Assistant Professor of Intensive Care, Department of Medical Intensive Care.
‡ Resident in Anesthesia, Department of Medical Intensive Care.
§ Senior Technician, Service d'Explorations Fonctionnelles.
¶ Assistant Professor of Physiology, Service d'Explorations Fonctionnelles.
** Professor of Medical Intensive Care, Department of Medical Intensive Care.

Received from the Department of Medical Intensive Care, the Service d'Explorations Fonctionnelles and INSERM U 296, Université Paris-Val de Marne and Henri Mondor University Hospital, 94010 Créteil cedex, France. Accepted for publication August 21, 1987. Supported by the Deutsche Forschungsgemeinschaft (grants RA 396/1-1 and FA 139/1-1) and the Ministerium für Wissenschaft und Forschung, Land NRW (Pr. 2702770).

Address reprint requests to Dr. Radermacher: Department of Anesthesiology, University of Düsseldorf, D-4000 Düsseldorf, FRG.

Key words: ARDS: Na-nitroprusside; pulmonary hypertension. Ketanserin: ventilation/perfusion distribution.

exchange during ketanserin infusion in patients with severe ARDS. We also compared the changes induced by ketanserin to those of SNP, a known pulmonary vasodilator.

Materials and Methods

Six consecutive patients (age 43.5 ± 18.3) without a history of previous lung disease were selected for this study. They met the clinical and radiological criteria for the diagnosis of ARDS:[13] 1) a ratio of arterial P_{O_2} to inspired oxygen fraction of less than 150; 2) a chest radiograph showing bilateral and diffuse parenchymal opacities; and 3) a compatible underlying disease (sepsis and/or infection).

All patients had pulmonary hypertension with a mean PAP equal to or greater than 25 mmHg. They were mechanically ventilated *via* an endotracheal tube with a volume-cycled ventilator (BEAR 1®, Bourns Inc., Riverside, CA) with a tidal volume (VT) of 10–12 ml/kg body weight at a respiratory rate of 16–18 breaths per minute and a mean FI_{O_2} of .81 (range .62–.99). The patients had thermodilution pulmonary artery catheters (Edwards® model 39A–131—7F, Santa Ana, CA) and radial or femoral arterial catheters inserted for continuous pressure recordings. Throughout the study, no cardiotonic or vasoactive drug was administered. All patients were sedated with intravenous fentanyl and flunitrazepam and paralyzed with pancuronium. According to the principles embodied in the Declaration of Helsinki, informed consent was obtained from next of kin before each study.

The following measurements were obtained in each patient: 1) tidal volume (VT) and minute ventilation (VE) using a calibrated spirometer (SE 302, Ohmeda®, Maurepas, France); 2) P_{O_2} of a gas sample from the inspiratory limb of the ventilator (ABL 30, Radiometer®, Copenhagen); arterial (a) and mixed venous *p*H, O_2 and CO_2 partial pressures (ABL 30); total hemoglobin and hemoglobin oxygen saturation (SO_2) by spectrophotometry (OSM 2, Hemoximeter, Radiometer, Copenhagen); 3) systemic and pulmonary vascular pressures (Hewlett-Packard transducers, model 1290 A, Andover, MA); cardiac output using a thermodilution cardiac output computer (Edwards, model 9520 A), the values reported being the mean of four to five determinations injecting dextrose at ambient temperature; and 4) continuous ventilation/perfusion ($\dot{V}_A/\dot{Q}$) distributions using the multiple inert gas elimination technique of Wagner *et al.*[14] as described previously.[15]

Systemic (SVRI) and pulmonary (PVRI) vascular resistance indices were calculated by standard formulas:

$$SVRI = (SAP - RAP)/CI$$

$$PVRI = (PAP - PAWP)/CI,$$

where SAP is the mean systemic arterial pressure, PAP the mean pulmonary artery pressure, RAP the right atrial pressure, PAWP the pulmonary artery wedge pressure, and CI the cardiac index.

Venous admixture was calculated according to Berggren's formula[16] after computing the alveolar P_{O_2} with the alveolar gas equation.

Protocol

Three successive sets of measurements were obtained while the levels of PEEP and FI_{O_2} were unchanged from maintenance values used before the study. Baseline values of hemodynamics, gas exchange, and inert gas elimination were measured prior to drug infusion. SNP infusion was then started (0.5–1.5 $\mu g/kg \cdot min$), and the infusion rate was adjusted to achieve a 30% (range 26–41%) reduction of mean systemic arterial pressure. Data were collected after 20 min had elapsed in stable conditions. Then SNP was discontinued, and, after another 20 min, hemodynamic measurements were obtained to assure that the patient had returned to the control values of the first data acquisition and that no rebound effects had occurred. Ketanserin was then administered as an iv bolus of 10 mg injected in 60 s, followed by an infusion at incremental rate over 30 min until a systemic blood pressure reduction equivalent to that which occurred during SNP infusion was obtained. Infusion rates up to 0.5 $mg \cdot kg^{-1} \cdot h^{-1}$ were required to obtain this effect. When stable conditions had been established, the third set of data was collected. The sequence of the drug administration was dictated by the longer and unpredictable half-life of ketanserin compared to SNP in our patients, which did not allow a cross-over study design.

Statistical evaluation was performed with a non-parametric Wilcoxon rank-sign test.[17] Significance was assumed if $P < 0.05$.

Results

Table 1 summarizes the hemodynamic and gas exchange effects of the SNP and ketanserin infusions in comparison to the control values. Both drugs provided equivalent reduction of SAP and of systemic vascular resistance index without altering cardiac output. Ketanserin did not alter the right atrial or the pulmonary artery wedge pressure, while SNP caused a significant fall of the PAWP without change of RAP. SNP infusion decreased mean PAP, from 30.7 ± 3.0 to 23.2 ± 3.9 mmHg ($P < 0.05$) and pulmonary vascular resistance index (PVRI) from 5.1 ± 1.8 to 4.2 ± 1.9 $mmHg \cdot min \cdot m^2/l$ ($P < 0.05$). Ketanserin slightly decreased mean PAP in all patients (to 27.8 ± 3.9 mmHg, $P < 0.05$), but did not alter the mean PVRI: PVRI

TABLE 1. Hemodynamic and Gas Exchange Data

	Control	SNP	Ketanserin
SAP (mmHg)	90.2 ± 26.2	62.7 ± 18.8*	65.0 ± 12.6*
RAP (mmHg)	8.7 ± 3.2	6.3 ± 3.9	9.8 ± 3.8
PAP (mmHg)	30.7 ± 3.0	23.2 ± 3.9*	27.9 ± 3.9*
PAWP (mmHg)	11.5 ± 2.7	7.5 ± 3.6*	7.3 ± 3.7
CI ($l \cdot min^{-1} \cdot m^{-2}$)	4.0 ± 1.1	4.0 ± 1.0	4.1 ± 1.2
SVRI ($mmHg \cdot min \cdot m^2/l$)	22.9 ± 13.4	15.5 ± 8.8*	15.6 ± 6.8*
PVRI ($mmHg \cdot min \cdot m^2/l$)	5.1 ± 1.8	4.2 ± 1.9*	4.9 ± 2.4
Pa_{O_2} (mmHg)	102.5 ± 48.9	65.5 ± 14.7*	87.3 ± 25.5
Pa_{CO_2} (mmHg)	38.0 ± 9.5	39.6 ± 9.9*	39.0 ± 10.7
$P\bar{v}O_2$ (mmHg)	41.2 ± 6.6	37.5 ± 5.4	41.2 ± 5.4
$\dot{V}O_2$ ($l \cdot min^{-1} \cdot m^{-2}$)	113.7 ± 26.2	105.4 ± 16.0	107.6 ± 17.5
$\dot{Q}_{VA}/\dot{Q}_T$ (%)	41.7 ± 11.0	52.4 ± 9.6*	45.7 ± 8.5

All data are mean ± SD. SAP = systemic arterial pressure; RAP = right atrial pressure; PAP = pulmonary artery pressure; PAWP = pulmonary artery wedge pressure; CI = cardiac index; SVRI = systemic vascular resistance indice; PVRI = pulmonary vascular resistance indice; $P\bar{v}O_2$ = mixed venous P_{O_2}; $\dot{V}O_2$ = calculated oxygen consumption; $\dot{Q}_{VA}/\dot{Q}_T$ = venous admixture.

* Significant difference ($P < 0.05$) for comparison between drug infusion and control values.

decreased in four patients; but, in the remaining two patients, the PAWP decreased, while CI decreased slightly, and an increased PVRI was computed.

SNP caused a dramatic fall of the arterial P_{O_2} (Pa_{O_2}) from 102.5 ± 48.0 to 65.5 ± 14.7 mmHg ($P < 0.05$), while venous admixture ($\dot{Q}_{VA}/\dot{Q}_T$) increased from 41.7 ± 11.0 to 52.4 ± 9.6 ($P < 0.05$). In contrast, ketanserin had no effect on Pa_{O_2} and $\dot{Q}_{VA}/\dot{Q}_T$ did not increase significantly. Neither drug significantly altered the mixed venous P_{O_2} ($P\bar{v}O_2$). The arterial P_{CO_2} increased slightly during SNP infusion, from 38.0 ± 9.5 to 39.6 ± 9.9 mmHg ($P < 0.05$), whereas it remained unchanged during ketanserin administration.

The inert gas analysis demonstrated that the high level of venous admixture in our patients (range 30.8–56.4%) was due to an increased right-to-left shunt ($\dot{Q}S/\dot{Q}T$) alone (n = 3), or a combination of shunt and of a perfusion fraction to low $\dot{V}A/\dot{Q}$ areas (n = 3) which ranged from 11.8–19.5% of the cardiac output. SNP infusion resulted in a marked increase of the $\dot{Q}_S/\dot{Q}_T$ (from 33.6 ± 13.2 to 42.4 ± 10.5%) (table 2), whereas the fractions of perfusion to low $\dot{V}A/\dot{Q}$ areas or to the central $\dot{V}A/\dot{Q}$ area were not significantly altered (fig. 1). The $\dot{V}A/\dot{Q}$ distribution was essentially unchanged during ketanserin infusion; $\dot{Q}_S/\dot{Q}_T$ increased in one patient, whereas it remained unchanged or decreased in the other patients. Dead space (V_D/V_T) increased during SNP infusion from 45.9 ± 7.5 to 51.8 ± 10.3%. A slight, but significant increase of V_D/V_T to 48.5 ± 9.0% was noted during ketanserin infusion.

DISCUSSION

Probable causes of pulmonary artery hypertension which occurs in ARDS include microembolism[18] and diffuse vasoconstriction.[7] This study was designed to compare, in the same group of patients, the effects on pulmonary hemodynamics and gas exchange of SNP, a potent vasodilator acting on vascular smooth muscle, and of ketanserin, a specific serotonin receptor antagonist, at doses achieving a comparable systemic vasodilating effect. This approach, and the use of the multiple inert gas elimination technique allowed us to selectively study their respective effects on pulmonary hemodynamics and explain the concommitent alterations of V_A/Q distribution. A comparison of the two drugs at doses achieving similar pulmonary vasodilation would have provided a more direct comparison of their respective effects on gas exchange, but this approach was not practical due to the limited effects of ketanserin and

TABLE 2. Inert Gas Elimination Data

	Control	SNP	Ketanserin
QS/QT	33.6 ± 13.2	42.4 ± 10.5*	33.3 ± 10.5
Low VA/Q	8.5 ± 9.7	3.8 ± 8.2	8.8 ± 5.9
Central $\dot{V}A/\dot{Q}$	55.8 ± 7.8	50.6 ± 8.5	56.2 ± 6.8
VD/VT	45.9 ± 7.5	51.8 ± 10.3*	48.5 ± 9.0*

All data are mean ± SD. QS/QT = right-to-left shunt; low $\dot{V}A/\dot{Q}$ = perfusion fraction to areas with $0.005 < VA/Q < 0.1$; central $\dot{V}A/\dot{Q}$ = perfusion fraction to areas with $0.1 < \dot{V}A/\dot{Q} < 10$; VD/VT = dead-space.

* Significant difference ($P < 0.05$) when drug infusion is compared to control values.

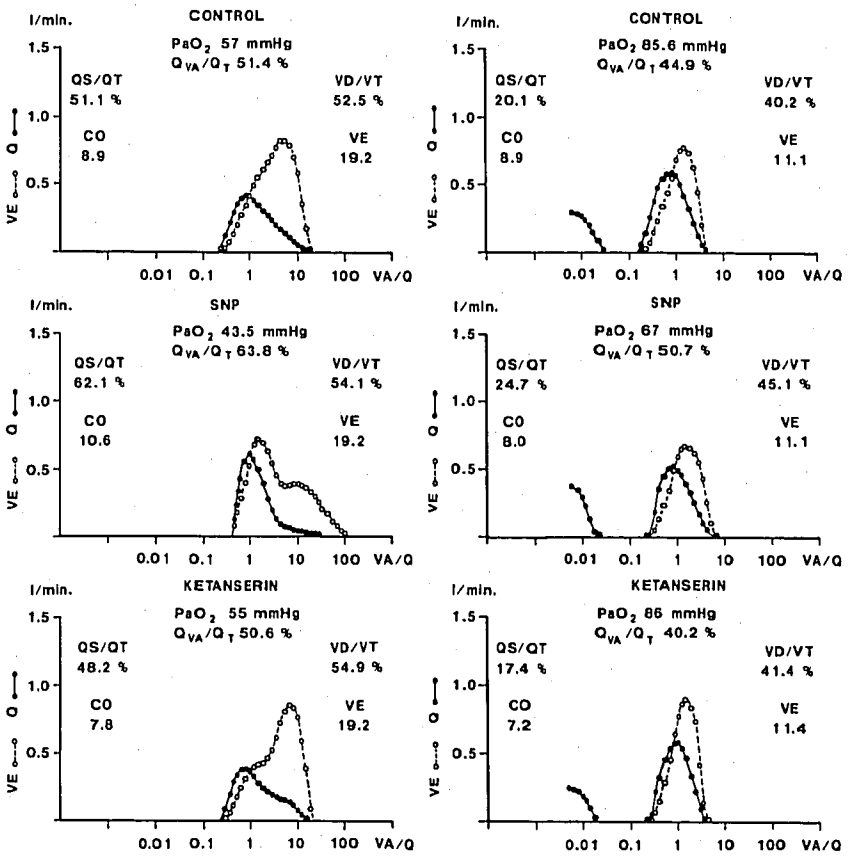

FIG. 1. Inert gas studies of two patients showing two different patterns of $\dot{V}_A/\dot{Q}$ distribution under control conditions (above) and during SNP (middle) and ketanserin infusion (below). On the left are the data from a patient with only true shunt ($\dot{Q}_S/\dot{Q}_T$) causing the large venous admixture ($\dot{Q}_{VA}/\dot{Q}_T$); on the right are data from another patient in whom shunt is associated with low $\dot{V}_A/\dot{Q}$ regions. Note the absence of change of $\dot{V}_A/\dot{Q}$ distribution during ketanserin infusion and the increase restricted to shunt ($\dot{Q}_S/\dot{Q}_T$) during SNP infusion.

its long half-life, which did not allow us to study ketanserin first. Infusing either drug resulted in a significant decrease of the mean PAP, although, at doses causing equal systemic vasodilation, ketanserin was a less potent pulmonary vasodilator than SNP. Thus, a reversible component of pulmonary vasoconstriction must have contributed to the pulmonary hypertension in our patients, since vasodilators are unlikely to reduce pulmonary hypertension secondary to microvascular destruction, as occurs in the advanced stages of ARDS.[7] Ketanserin may have lowered PAP by two mechanisms: the inhibition of serotonin and/or the blockade of alpha$_1$-adrenergic receptors, as suggested by Fozard.[19] At the dosage we used, both mechanisms may account for the hemodynamic effect of ketanserin.[20] Whatever the mechanisms involved, the fact that ketanserin induced less pulmonary artery dilation than SNP suggests that vasoconstrictor agents other than serotonin, such as thromboxane[21] or leukotrienes,[22] are also responsible for the pulmonary hypertension in ARDS.

All of our patients had a large venous admixture which was attributed by inert gas analysis to both shunt alone or a combination of shunt and low V_A/Q areas. These data are similar to those reported by Matamis *et al.*[15] and by Ralph *et al.*,[23] who analyzed the effect of PEEP ventilation in ARDS patients. The marked increase of venous admixture we measured during SNP infusion in our patients confirms data obtained from a canine model of oleic acid-induced lung injury[24] and in patients with ARDS.[6,7] The inert gas elimination analysis showed that the increased venous admixture caused by SNP in our patients was due to a significant increase of the right-to-left shunt, whereas the perfusion fraction to the low V_A/Q area was unchanged (fig. 1). In a canine model of ARDS induced by oleic acid,[25] Colley *et al.* obtained similar results. In some of the dogs, SNP infusion caused little effect on Q_S/Q_T, but increased perfusion to the low V_A/Q area; whereas, in other animals, the right-to-left shunt increased during SNP infusion.

In our patients, SNP did not alter two of the important determinants of $\dot{Q}_S/\dot{Q}_T$, cardiac output,[26] and $P\bar{v}O_2$.[27] These results, and the reduction of the perfusion to the central $\dot{V}_A/\dot{Q}$ area, suggest that the increase of the right-to-left shunt was due to a redistribution of pulmonary blood flow to unventilated lung regions. This shift of the pulmonary blood flow distribution is probably due to the inhibition of hypoxic pulmonary vasoconstriction, as demonstrated during one-lung anesthesia.[28] The shift of pulmonary blood flow to hypo-

and unventilated lung regions also explains the increased dead space ventilation during SNP infusion. Furthermore, the reduction of mean PAP probably partly derecruited the pulmonary vasculature, increasing zone I areas and, thus, alveolar dead space. As total minute ventilation and cardiac output did not change throughout the study, the increased dead space resulted in a significant increase of Pa_{CO_2}.

The multiple inert gas analysis showed that ketanserin infusion dilated the pulmonary vascular bed without notably altering $\dot{V}_A/\dot{Q}$ matching. The statistically non-significant increase in $\dot{Q}_{VA}/\dot{Q}_T$ (to 45.7 ± 8.5%) during ketanserin infusion (table 1) was probably due to an increased $\dot{Q}S/\dot{Q}T$ in one patient, whereas it remained unchanged or decreased in the other patients. Vincent *et al.*[11] and Olson[20] hypothetized that ketanserin may relieve airway constriction in hypoventilated lung areas. Alveolar ventilation in such regions would then be improved, compensating for a pulmonary vasodilator effect, thereby providing an unchanged $\dot{V}_A/\dot{Q}$ distribution. With the central $\dot{V}_A/\dot{Q}$ area unchanged during ketanserin infusion, the increase of dead space ventilation was too small to yield a significant change of Pa_{CO_2}.

Our results that ketanserin did not increase Pa_{O_2} or reduce $\dot{Q}_{VA}/\dot{Q}_T$ differ from previous studies.[11,12] This may be due to the greater severity of acute lung injury in our patients; whereas they had a mean $\dot{Q}_{VA}/\dot{Q}_T$ of 41.7%, with the lowest value over 30%, the mean $\dot{Q}_{VA}/\dot{Q}_T$ values in the studies of Vincent *et al.*[11] and Huval *et al.*[12] were 27%. Severe pulmonary microvascular injury may lessen the responsiveness to ketanserin, or perhaps ketanserin is no longer effective as a pulmonary vasodilator in advanced ARDS. This hypothesis was suggested by Huval *et al.*,[12] who noted that ketanserin was ineffective when administered to patients whose tracheas were intubated for more than 4 days. Huet *et al.*[29] observed a decrease in $\dot{V}O_2$ during ketanserin infusion in patients with acute pulmonary embolism, and suggested that this may beneficially influence arterial oxygenation. In our patients, the calculated $\dot{V}O_2$ did not vary throughout the study.

We conclude that SNP efficiently lowers PAP in patients with severe ARDS, indicating that pulmonary vasoconstriction persists, even in the advanced stage of the disease. Its clinical use, however, cannot be recommended because SNP markedly impairs pulmonary gas exchange by increasing $\dot{Q}_{VA}/\dot{Q}_T$. The increased $\dot{Q}_{VA}/\dot{Q}_T$ is caused by an increased $\dot{Q}_S/\dot{Q}_T$ due to a redistribution of pulmonary blood flow. Possibly because a less potent pulmonary vasodilator than SNP, ketanserin has no deleterious effects on gas exchange. Ketanserin administration may be useful in patients with ARDS, especially when given early in the course of the disease.

The authors thank Mrs. A. Dupeyrat for her skilful technical assistance, Mr. A. Rauss for advice with the statistical analysis, Mrs. M. Guérin and Mrs. F. Delcampe for typing the manuscript, and Dr. C. Brun-Buisson for reviewing it. They are indebted to Jacques Dulleroy and Bruno Fraitag, M.D., (Janssen Laboratories) for supplying ketanserin.

References

1. Zapol WM, Snider MT: Pulmonary hypertension in severe acute respiratory failure. N Engl J Med 296:476–480, 1977
2. Sibbald WJ, Driedger AA, Myers ML, Short AIK, Wells GA: Biventricular function in the adult respiratory distress syndrome. Chest 84:126–134, 1983
3. Brigham KL, Wolverton WC, Blake LH, Staub NC: Increased lung vascular permeability caused by Pseudomonas bacteremia. J Clin Invest 54:792–804, 1974
4. Erdmann JA III, Vaughan TR Jr, Brigham KL, Woolverton WC, Staub NC: Effect of increased intravascular pressure on lung fluid balance of anesthetized sheep. Circ Res 37:271–284, 1975
5. Prewitt RM, McCarthy J, Wood LDH: Treatment of acute low pressure pulmonary edema in dogs. J Clin Invest 67:409–418, 1981
6. Weigelt JA, Gewertz BL, Aurbakken CM, Snyder WH: Pharmacologic alterations in pulmonary artery pressure in the adult respiratory distress syndrome. J Surg Res 32:243–248, 1982
7. Zapol WM, Snider MT, Rie MA, Frikker M, Quinn DA: Pulmonary circulation during adult respiratory distress syndrome. Acute respiratory failure. Edited by Zapol WM, Falke KJ. New York, Dekker, 1985, pp 241–273
8. Sibbald WJ, Peters S, Lindsay RM: Serotonin and pulmonary hypertension in human septic ARDS. Crit Care Med 8:490–494, 1980
9. Schneider R, Zapol WM, Carvalho A: Platelet consumption and sequestration in severe acute respiratory failure. Am Rev Respir Dis 122:445–451, 1980
10. Van Nueten JM, Janssen PAJ, Vanbeek J, Xhonneur R, Verbeuten TJ, Vanhoutte PM: Vascular effects of R 41468, a novel antagonist of 5-HT2 serotonergic receptors. J Pharmacol Exp Ther 218:217–230, 1981
11. Vincent JL, Degaute JP, Domb M, Simon P, Berre J, Vendersteene A: Ketanserin, a serotonin antagonist. Chest 85:510–513, 1984
12. Huval WV, Lelcuk S, Sherpo D, Hechtman HB: Role of serotonin in patients with acute respiratory failure. Ann Surg 200:166–172, 1984
13. Rinaldo JE, Borovetz HS, Mancini MC, Hardesty RL, Griffith BP: Assessment of lung injury in the adult respiratory distress syndrome using multiple indicator dilution curves. Am Rev Respir Dis 133:1006–1010, 1986
14. Wagner PD, Saltzmann HA, West JB: Measurement of continuous distributions of ventilation perfusion rations: Theory. J Appl Physiol 36:588–599, 1974
15. Matamis D, Lemaire F, Harf A, Teiseire B, Brun-Buisson C: Redistribution of pulmonary blood flow induced by positive end-expiratory pressure and dopamine infusion in acute respiratory failure. Am Rev Respir Dis 129:39–44, 1984
16. Berggren S: The oxygen deficit of arterial blood caused by non-

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.