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Effects of Ketamine and Halothane on Increased Respiratory Resistance Provoked by Ultrasonic Aerosols

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The effects of halothane and ketamine on respiratory resistance and compliance were determined in anesthetized, intubated patients in whom respiratory resistance was artificially increased by ultrasonic aerosols. Halothane caused a prompt decrease in respiratory resistance with no change in compliance. Ketamine had no effect on resistance. Isoproterenol given to the subjects who did not respond to ketamine resulted in a rapid decrease in resistance to control levels. Ketamine decreased compliance in subjects with normal or increased respiratory resistance. We conclude that halothane remains a useful drug for patients who have increased respiratory resistance. Any utility of ketamine in anesthetic management of asthmatic patients must be on a basis other than a bronchodilator side-effect. (Key words: Anesthetics, intravenous, ketamine; Anesthetics, volatile, halothane; Lung, respiratory resistance; Airway, resistance.)

HALOTHANE is widely accepted as the agent of choice for anesthetic management of patients with bronchospasm. Recently, Corssen et al.[1] advocated using ketamine in the management of asthmatic patients. There are few experimental clinical data to support either of these views, and the management of patients with bronchospasm remains primarily empirical.

Respiratory resistance is increased by endotracheal administration of ultrasonic aerosols of water or saline solution.[2,3] This increased resistance is promptly reversed by isoproterenol and thus is thought to be caused by increased bronchial tone.[3] This study was designed to increase respiratory resistance of anesthetized patients using ultrasonic mist and to evaluate the effects of halothane and ketamine on this increased resistance.

Methods

Twenty consenting adult surgical patients who required general endotracheal anesthesia for lower abdominal operations were studied. Patients having histories of bronchopulmonary disease were excluded. Anesthesia was induced with thiopental (sufficient to abolish lid reflex) and was maintained with N_2O, 70 per cent, in oxygen. The anesthesia was supplemented with meperidine, 2.5 mg/kg, and *d*-tubocurarine, 0.4–0.6 mg/kg, prior to the start of operation.

Compliance and resistance for the total respiratory system were derived from flow, volume, and transthoracic pressure measurements obtained during thoracic inflation and subsequent passive exhalation by a previously described method.[4] The subject's lungs were inflated with 1 liter of gas. When airway pressure stabilized, indicating complete and even distribution of the gas, a valve in the expiratory line was opened and the patient exhaled into a waterless spirometer ("Wedge," Med-Science, St. Louis). The spirometer transducers provided simultaneous expiratory flow and volume tracing. The transthoracic pressure at 0.5 l/sec flow was calculated by dividing the volume remaining in the lungs at this instant by compliance. From this flow rate and simultaneous pressure, respiratory resistance may be calculated. All resistance data are in cm H_2O/l/sec at 0.5 l/sec flow. All compliance data are ml/cm H_2O at 1,000 ml above functional residual capacity. The data for any subject in

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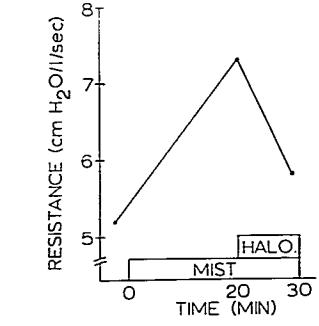

FIG. 1. Effect of halothane on increased respiratory resistance provoked by ultrasonic mist, Group I.

TABLE 1. The Effect of Halothane after a Provoked Increase in Respiratory Resistance, Group I

Subject	Age (Years)	Control C*	Control R†	Mist C	Mist R	Halothane C	Halothane R
1	30	64	4.2	60	4.7	57	4.1
2	22	69	6.3	49	8.7	48	8.1
3	35	53	5.8	45	8.0	51	6.6
4	17	46	5.4	46	9.5	43	5.2
5	25	77	4.3	80	5.6	73	4.7
Mean	—	62	5.2	56	7.3	54	5.8
SD	—	12.5	0.94	14.7	2.07	11.5	1.61

* Respiratory compliance (ml/cm H_2O).
† Respiratory resistance (cm H_2O/l/sec).

any situation are the mean of five separate determinations made at 3-minute intervals.

Subjects were divided into four groups. "Control" studies were done 5 minutes after surgical stimulation had begun to include any possible bronchodilator effects from catecholamine release.

In Group I (table 1, fig. 1), after the "control" measurements, the inspired gas mixture was humidified with an ultrasonic nebulizer (Monaghan, 670). This unit was placed in the inspiratory limb of the circuit and set to deliver 1.5 ml of either sterile water or saline solution per minute as mist. The subjects were ventilated with this humidified gas mixture for 20 minutes, and then five further measurements of respiratory mechanics were made at 3-minute intervals. Halothane (1.0–2.0 per cent) was then added to the mist–gas mixture and continued until systolic blood pressure decreased 20 per cent, at which time measurements of respiratory mechanics were repeated.

In Group II (table 2, fig. 2), the "control" and "mist" studies were done as described above. The mist was continued and subjects were then given ketamine, 2 mg/kg, intravenously. Studies of respiratory mechanics were made 1, 2, 3, 5, and 7 minutes after injection. These subjects were then given two metered doses of isoproterenol mist from a Medihaler (Isuprel, 4 mg/ml) and after tachycardia developed, respiratory mechanics were again studied.

Groups III and IV were not given mist. After "control" studies they were given ketamine, 2 mg/kg, intravenously, and the studies repeated as described for Group II. In group III control resistance was less than 9 cm H_2O/l/sec, and it was more than this in Group IV. Resistance above this level is

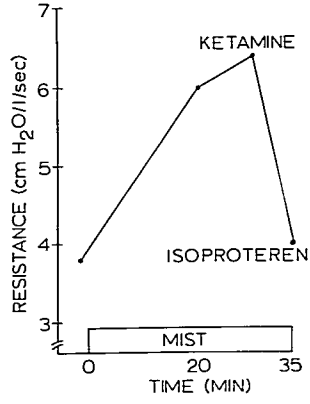

FIG. 2. Effects of ketamine and isoproterenol on increased respiratory resistance provoked by ultrasonic mist, Group II.

TABLE 2. Effects of Ketamine and Isoproterenol after a Provoked Increase in Respiratory Resistance, Group II

Subject	Age (years)	Control		Mist		Ketamine		Isoproterenol	
		C*	R†	C	R	C	R	C	R
1	30	79	2.9	75	5.7	75	5.3	76	3.5
2	23	97	3.3	104	4.9	104	5.1	102	3.4
3	40	83	4.5	63	6.9	65	7.4	68	4.3
4	54	87	4.8	82	8.5	80	9.1	82	5.5
5	36	104	3.3	119	4.1	116	4.9	114	3.1
Mean		90	3.8	88	6.0	88	6.4	88	4.0
SD		10.3	.84	22.6	1.73	21.2	1.83	19	.97

* Respiratory compliance (ml/cm H_2O).
† Respiratory resistance (cm H_2O/l/sec).

associated with pulmonary dysfunction in asymptomatic subjects.[4]

Statistical evaluation was by paired t test.

Results

The results are summarized in figures 1 and 2 and the individual data are listed in the tables. In Group I (table 1, fig. 1) 20 minutes of ventilation with mist increased resistance from 5.2 (SD = 0.94) to 7.3 (SD = 2.07) H_2O/l/sec ($P < .025$). Following halothane, resistance decreased to 5.8 (SD = 1.61) H_2O/l/sec ($P < .05$). Respiratory compliance was not changed by mist or by halothane.

In Group II (table 2, fig. 2) 20 minutes of ventilation with mist increased resistance from 3.8 (SD = .84) to 6.0 (SD = 1.73) H_2O/l/sec ($P < .01$). Ketamine, 2 mg/kg, intravenously, had no effect on resistance, but after isoproterenol resistance decreased to 4.0 (SD = .97) H_2O/l/sec ($P < .005$). Neither mist nor ketamine nor isoproterenol affected respiratory compliance.

Ketamine given to subjects with normal respiratory resistance (Group III, table 3) did not change resistance, but decreased compliance from 78 (SD = 17.8) to 74 (SD = 15.9) ml/cm H_2O ($P < .025$). In subjects with control resistances greater than 9 cm H_2O/l/sec (Group IV, table 4), ketamine did not change resistance, but did decrease compliance from 56 (SD = 10.7) to 54 (SD = 10) ml/cm H_2O ($P < .025$).

There was no postoperative problem that could be attributed to the study procedure.

TABLE 3. The Effect of Ketamine on Respiratory Mechanics in Patients with Normal Respiratory Resistance, Group III

Subject	Age (years)	Control		Ketamine	
		C*	R†	C	R
1	49	68	8.4	64	7.1
2	29	63	7.0	62	7.4
3	59	75	4.9	72	5.3
4	36	109	7.9	99	10.6
5	47	88	5.1	86	5.1
6	24	65	6.3	58	5.7
Mean	—	78	6.6	74	6.9
SD	—	17.8	1.45	15.8	2.07

* Respiratory compliance (ml/cm H_2O).
† Respiratory resistance (cm H_2O/l/sec).

TABLE 4. The Effect of Ketamine on Respiratory Mechanics in Patients with Increased Respiratory Resistance, Group IV

Subject	Age (years)	Control		Ketamine	
		C*	R†	C	R
1	64	48	14.1	47	15.1
2	68	70	14.9	67	16.6
3	36	60	13.6	56	13.7
4	48	47	12.6	45	12.1
Mean	—	56	13.8	54	14.8
SD	—	10.7	0.97	10.0	1.95

* Respiratory compliance (ml/cm H_2O).
† Respiratory resistance (cm H_2O/l/sec).

Discussion

Ultrasonic aerosols of water or saline solution significantly increase respiratory resistance when delivered directly into the airway. This is independent of the composition of the mist,[3] is not progressive, and persists for variable periods sometimes as long as 30 minutes after the mist is stopped.[2] It is unlikely that accumulation of mist liquid caused the increased resistance, as fluids are absorbed very rapidly from the airway[5] and the total amount of fluid given to our subjects rarely exceeded 50 ml in a 30-minute period. The response of our patients, and those in a previous study,[3] to isoproterenol indicates that the increased resistance after intratracheal aerosols is largely due to increased bronchial tone. Thus, we believe this technique provides a model in which to study the effect of anesthetics on increased respiratory resistance.

Halothane promptly decreases increased respiratory resistance provoked by ultrasonic aerosols. This confirms the clinical impression that halothane decreases respiratory resistance in patients with bronchospasm.[6] Klide and Aviado[7] found, in dogs, that the decrease in pulmonary resistance caused by halothane was blocked by a beta-adrenergic blocking agent, and on this basis concluded that halothane stimulates beta receptors in the airway.

Our failure to find a bronchodilator effect with ketamine is at variance with findings of others. Corssen and others[1,8] reported that ketamine relieves acute bronchospasm almost immediately, and that this effect lasts 10 minutes. They postulated that the bronchodilator effect of ketamine is secondary to the increased plasma norepinephrine level known to occur with ketamine. However, a recent study raises doubt as to whether norepinephrine does in fact have a bronchial muscle relaxant action.[9] The prompt decrease in resistance in our subjects given isoproterenol after ketamine indicates that if ketamine does indeed have a bronchodilator action, it should have been manifest. Cardiac arrhythmias did not occur following isoproterenol mist.

We were also unable to confirm the improved respiratory compliance following ketamine administration reported by others.[10] In subjects given ketamine without prior challenge by ultrasonic mist (Groups III and IV) there was a minimal but statistically significant decrease in compliance. The subjects with artificially increased resistance had no change in compliance after ketamine.

We conclude that the increased resistance produced by ultrasonic mist is rapidly reversed by a bronchodilator (isoproterenol) and an anesthetic (halothane), each of which is known to relieve bronchospasm in asthmatic patients. We found no similar action for ketamine.

References

1. Corssen G, Gutierrez J, Reves JG, et al: Ketamine in the anesthetic management of asthmatic patients. Anesth Analg (Cleve) 51:588–596, 1972
2. Waltemath CL, Bergman NA: Increased respiratory resistance provoked by endotracheal administration of aerosols. Am Rev Resp Dis 108:520–525, 1973
3. Waltemath CL, Erbguth PH, Sunderland WA: Increased respiratory resistance after ultrasonic humidification of anesthesia gas. ANESTHESIOLOGY 39:547–549, 1973
4. Bergman NA: Properties of passive exhalations in anesthetized subjects. ANESTHESIOLOGY 30:378–387, 1969
5. Modell JH, Moya F: Effects of aspirated fluid during chlorinated fresh water drowning. ANESTHESIOLOGY 27:662–672, 1966
6. Shnider SM, Papper EM: Anesthesia for the asthmatic patient. ANESTHESIOLOGY 22:886–892, 1961
7. Klide AM, Aviado DM: Mechanism for the reduction in pulmonary resistance induced by halothane. J Pharmacol Exp Ther 158:28–35, 1967
8. Huber FC Jr, Reves JG, Gutierrez J, et al: Ketamine: Its effect on airway resistance in man. South Med J 65:1176–1180, 1972
9. Stone DJ, Sarkar TK, Keltz H: Effect of adrenergic stimulation and inhibition of human airways. J Appl Physiol 34:624–627, 1973
10. Corssen G, Domino EF: Dissociative anesthesia: Further pharmacologic studies and first clinical experience with the phencyclidine derivative. CI-581. Anesth Analg (Cleve) 45:29–40, 1966