THE EFFECT OF METHOXYFLURANE ON BAROREFLEX CONTROL OF HEART RATE IN MAN

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THE PURPOSE OF THIS STUDY was to assess the function of the baroreceptor reflex under methoxyflurane anaesthesia, using the pressor test.

The baroreceptor reflex is an important regulator of blood pressure in man. The carotid and aortic baroreceptors comprise the principal sensory input of the baroreflex.¹ Baroreceptor impulses are carried by cranial nerves ix and x to the vasomotor center in the medulla oblongata. Baroreceptor impulses inhibit sympathetic discharge and facilitate vagal firing. The efferent limb of the reflex arc is carried by autonomic neurones to resistance vessels, capacitance vessels, and the heart. A hypotensive stress (e.g. hypovolaemia) reflexly induces tachycardia, increased myocardial contractility, and peripheral vasoconstriction of resistance and capacitance vessels. A hypertensive stress reflexly induces bradycardia, decreased myocardial contractility, and peripheral vasodilation of resistance and capacitance vessels. Without baroreflex function, fine control of the circulation is lost,² the body being unable to compensate for hypertension and hypotension.

Smyth *et al.* described the pressor test in 1969.³ They showed that baroreflex function in man can be quantitated in terms of degree of cardiac slowing in response to transient increases in blood pressure. Angiotensin amide causes transient increases in blood pressure, by stimulating vasoconstriction at pre-capillary sphincters of the skin, the splanchnic region, and the kidney. The standard dose is approximately 4 μ g, which acts in about 30 seconds to raise systolic blood pressure 20–30 torr for 1.5 minutes. Blood pressure, ECG, and phases of respiration are simultaneously recorded from the time of injection of angiotensin until peak pressure is achieved. Each increasing systolic pressure is then plotted in a beat to beat fashion against its succeeding R-R interval (Figure 1). Pulse intervals during inspiration are excluded in order to avoid the effect of sinus arrhythmia. Utilizing the least squares to fit of points (Figure 2), the results are expressed as a line. The line has a slope measured in msec. increase in R-R interval/torr rise in systolic blood pressure and is an index of baroreflex function. The more sensitive the reflex, the steeper the slope of the line. The baroreflex is "reset" during anaesthesia, when resting blood pressure is maintained at an elevated or lowered state.⁴ With the pressor test, this resetting is seen as a change in position of the line, with or without a change in slope. With the pressor test, the patient serves as his own control when conscious, and the control slope is compared to the slopes obtained at different levels of anaesthesia.

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FIGURE 1

FIGURE 2

METHOD

Seven healthy patients (2 female, 5 male) undergoing minor ENT surgery were studied. Their ages ranged from 24 to 37 years, with an average of 28 years. All subjects signed a consent form acknowledging their understanding and approval of the procedure. The subjects arrived in the OR unpremedicated, two hours prior to surgery. An intravenous infusion (Jelco No. 18) was started and an intra-arterial catheter (Argyle Medicut No. 18) was inserted into the radial artery under local anaesthesia. Radial artery pressure was recorded using a pressure transducer (Stratham Pb23), which led to a four channel recorder (Electronics for Medicine). EKG leads were placed on the patient and connected to the recorder.

The ventilation of the conscious patient was controlled at a comfortable breathing rate and tidal volume, using an Ohio anaesthesia ventilator (Model 300) placed in a semi-closed anaesthetic circuit. The patient breathed 100 per cent O_2 , and nose-plugs and a mouthpiece prevented escape of gases. Phases of respiration were determined with the recorder and a pressure transducer (Stratham Pb23) connected to the patient's airway.

Prior to anaesthesia the pressor test was performed in duplicate (control runs) and blood gases were sampled.

A mask induction was performed with methoxyflurane/ O_2 . Succinylcholine (60-80 mg) was given intravenously and the trachea was intubated. Respiratory

rate and tidal volume remained the same as during the control period. End tidal (alveolar) gases were sampled; methoxyflurane concentration was measured with an infra-red analyzer (Beckman IR 215). The pressor test was performed in duplicate at two set ranges of methoxyflurane concentration, 1.5 MAC (.225 per cent - .25 per cent alveolar methoxyflurane) and 2 MAC (.275 per cent-.325 per cent alveolar methoxyflurane).⁵ Subjects were allowed to reach a steady state at a given alveolar concentration of methoxyflurane, to assure cerebral equilibration. Blood gases were sampled during anaesthesia. The pressor tests were analyzed using Smyth's method.⁸

RESULTS

Table I presents data from all seven patients. Poor correlation coefficients for certain slopes ($< .78$) resulted in no data reported in 3 cases; patient No. 5 - 1.5 MAC slope, patient No. 1 and 4 - 2 MAC slope. Using a paired t test each patient's control slopes were compared against his anaesthetized slopes (1.5 MAC and 2 MAC). No significant difference existed between the control and anaesthetized slopes in each of the seven subjects.

Data from six patients anaesthetized to the depth of 1.5 MAC was combined and compared to control values (Table II). Mean control slope was 22.8 ± 12.5 and the mean anaesthetized slope was 25.3 ± 11.9 . Using a paired t test ($p .05$) no significant difference was shown to exist between mean control slope, and the slope at 1.5 MAC. Mean resting systolic blood pressure decreased from 121 torr to 92 torr (1.5 MAC) and this was significant statistically. Mean heart rate, PaO_2 , Paco_2 and pH remained constant.

Patient	CONTROL				1.5 M.A.C.				2 M.A.C.			
	Slope	B.P.	H.R.	No. of Runs	Slope	B.P.	H.R.	No. of Runs	Slope	B.P.	H.R.	No. of Runs
1. Male	48 ± 4	130 $\pm$ 5	66 $\pm$ 2	2	48	80	68	1	-	-	-	-
2. Female	20 ± 6	92 $\pm$ 1	62 $\pm$ 2	2	25	61	60	1	19 $\pm$ 3	60 $\pm$ 0	66 $\pm$ 2	2
3. Male	19.5 ± 5	129 $\pm$ 1	72 $\pm$ 4	2	19.1	100	68	1	19.1	100	68	1
4. Male	15.0 ± 5	145 $\pm$ 2	60 $\pm$ 0	2	15.8 $\pm$ 2	126 $\pm$ 2	66 $\pm$ 2	2	-	-	-	-
5. Male	15.5 ± 1	127 $\pm$ 1	58 $\pm$ 2	2	-	-	-	-	11.5 $\pm$ 1	102 $\pm$ 0	56 $\pm$ 0	2
6. Male	18 ± 5	107 $\pm$ 5	54 $\pm$ 2	2	17.0 $\pm$ 1	92	60	1	13.2 $\pm$ 2	93 $\pm$ 3	64 $\pm$ 4	3
7. Female	16.6 ± 1	121 $\pm$ 1	55 $\pm$ 3	3	27.1	91	64	1	16.8	84	64	1

		Blood Gases					
		Slope	B.P.	H.R.	PO_2	PCO_2	pH
		Mean S.D.	Mean S.D.	Mean S.D.	Mean S.D.	Mean S.D.	Mean S.D.
1.5 M.A.C. 6 Patients	Control	22.8 ± 12.5	121 $\pm$ 18	61 $\pm$ 7	540 $\pm$ 33.8	31 $\pm$ 7.6	7.40 $\pm$.087
	Anesthetized	25.3 ± 11.9	92 $\pm$ 21	64 $\pm$ 3	526 $\pm$ 56	31 $\pm$ 9.0	7.46 $\pm$.077
2 M.A.C. 5 Patients	Control	17.9 ± 1.9	115 $\pm$ 15	60 $\pm$ 1	536 $\pm$ 30	32 $\pm$ 8	7.49 $\pm$.08
	Anesthetized	15.9 ± 3.4	88 $\pm$ 17	63 $\pm$ 5	519 $\pm$ 60	32 $\pm$ 10	7.46 $\pm$.06

Data from five patients anaesthetized to the depth of 2 MAC was combined in the same manner. Mean control slope was 17.9 ± 1.9 , and the mean anaesthetized slope was 15.9 ± 3.4 . Using a paired *t* test no significant difference was shown to exist between mean control slope and the mean slope at 2 MAC. Mean resting systolic blood pressure decreased from 115 torr to 88 torr (2 MAC) and this was significant statistically. Mean heart rate, PaO_2 , PaCO_2 , and pH remained constant.

Figures 3 and 4 are graphical illustration of the slopes in Table II. Although mean RR drops significantly, there is no significant difference between control and anaesthetized slopes. The shaded area represents 1SD on each side of the mean slope.

DISCUSSION

From these data we conclude that methoxyflurane anaesthesia does not alter the sensitivity of the baroreceptor reflex, as measured by the pressor test. Methoxyflurane anaesthesia lowered resting blood pressure significantly at these anaesthetic concentrations. Thus, the baroreflex is reset to the left. Previous studies have shown that halothane at 1 MAC (.7 per cent) diminishes baroreflex sensitivity by approximately 75 per cent, and abolishes it at 1.5 MAC (1.2 per cent).^{4,6} Halothane also lowers blood pressure during anaesthesia, thus resetting the baroreflex. Because methoxyflurane preserves, and halothane abolishes baroreflex sensitivity, it may be preferable to halothane in clinical situations where sudden changes in posture (e.g. pneumoencephalogram) or extensive haemorrhage occur.

We used the pressor test to determine the effect of methoxyflurane on the baroreflex arc. This test can be criticized because it only measures one part of the

baroreflex (heart rate), and this part is only measured in response to a hypertensive stimulus.

Using the pressor test, our group has studied the effect of age, 100 per cent O_2 , controlled ventilation, and halothane anaesthesia on the baroreflex.^{6,7} Smyth, Bristow, *et al.*^{3,4,8} have used the pressor test to study the effect of sleep, hypertension, and certain anaesthetic agents on the baroreflex. The anaesthetic agents studied were halothane and nitrous oxide, and thiopentone. In contrast to their study, we attempted to control certain variables. Premedication with atropine and demerol was spared because these drugs could interfere with assessment of baroreflex function at a given MAC. Blood gases were controlled to avoid contributions from the aortic and carotid bodies. The MAC concept¹⁰ was utilized in selecting the depth of anaesthesia to enable comparison with other agents at equipotent doses.

SUMMARY

Using the pressor test, the effects of methoxyflurane on the setting and sensitivity of the baroreflex were studied in man. At 1.5 MAC methoxyflurane, the slope (25.3 ± 11.9) did not differ significantly from the control slope (22.8 ± 12.5). At 2 MAC the slope (15.9 ± 3.4) did not differ significantly from the control slope (17.9 ± 1.9). At both concentrations of methoxyflurane, resting systolic blood pressure decreased significantly (27–39 mm Hg). Thus, methoxyflurane resets the baroreflex to the left, but does not alter its sensitivity.

RÉSUMÉ

En nous servant du test de la pression, nous avons étudié chez l'homme l'effet

du méthoxyflurane sur le déclenchement et la sensibilité des baroréflexes. A 1.5 MAC de méthoxyflurane la courbe (25.3 ± 11.9) n'a pas varié tellement de la courbe des contrôles (22.8 ± 12.5). A 2 MAC la courbe (15.9 ± 3.4) n'a pas varié beaucoup de la courbe des contrôles (17.9 ± 1.9). Aux deux concentrations de méthoxyflurane, la pression sanguine systolique au repos a diminué sensiblement ($25 - 39$ mm Hg). Ainsi, peut-on dire, le méthoxyflurane déplace les baroréflexes vers la gauche mais n'affecte pas sa sensibilité.

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