COMPARISON OF CARDIOVASCULAR, RESPIRATORY, AND METABOLIC EFFECTS OF HALOTHANE-ETHER AZEOTROPIC MIXTURE WITH THOSE OF METHOXYFLURANE ANAESTHESIA IN MAN*

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Since its introduction by Hudon, the halothane-ether azeotropic mixture has earned a place of its own in the armamentarium of anaesthesia Numerous studies have given detailed consideration to the clinical aspects of its administration and stated factual information about its convenience, safety, and virtual lack of unpleasant side-effects Adverse comments and controversial attitudes, sometimes based on casual trial, nonetheless bespeak the influence exerted by this azeotrope among other established agents Particular attention has been given to its cardiovascular actions by Wyant,[1] Dobkin,[2] Déchêne[3] and their collaborators The interpretation of their measurements, however, remains difficult because their studies are purely pharmacological, conducted outside the operating room and in known artificial conditions The validity of their methods rests on solid foundations, and this study does not intend to refute their conclusions However, their results can hardly be said to be those which one will encounter in daily practice Everybody will agree that surgery is a far greater physiological stress to the patient than anaesthesia, and this fact should not be ignored when one is dealing with the respiratory and cardiovascular activity of patients who, usually, are anaesthetized for and during surgery

The purpose of this report is to evaluate the various physiological responses associated with the administration of halothane-ether azeotrope in patients who at the same time were submitted to minor surgical procedures The virtue of this approach, as stressed by Price,[4] is that it describes changes which occur under conditions likely to met in everyday practice In a preceding paper, we have described the pharmacological effects of methoxyflurane during surgical anaesthesia in man [5] As both studies were conducted in exactly the same way, we shall take the opportunity to draw a comparison between these two drugs

Materials and Methods

The experiments were carried out on 20 patients, 7 males and 13 females Their mean age was 45 3 years, the extremes being 21 and 76 years History, physical examination, X-rays of the chest, and electrocardiogram were obtained in all patients, along with routine laboratory tests, and revealed no evidence of

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organic systemic disease Haemodynamic and respiratory studies were conducted in 9 of these patients, and additional data pertinent to metabolic and endocrine functions were obtained from 11 other patients anaesthetized under similar conditions

The method used has been described in a previous publication[5] Briefly, it involved the serial determination, before, during, and after anaesthesia, of

(*a*) *Pulmonary ventilation* This was obtained from a Wright Ventilometer attached to the mask and located in front of the rebreathing circle

(*b*) *CO_2 concentrations in expired gas* This was monitored continuously on the Godart Capnograph and recorded on the Omniascriptor CO_2 output per minute was obtained from planimetric measurement of the area under the curve of CO_2 concentration

(*c*) *Arterial and mixed venous blood gas tensions* Arterial blood was collected through a 21-gauge Lindeman needle inserted into the brachial artery, mixed venous blood was obtained from a PE catheter 20 inches long fed through a 15-gauge needle driven into an elbow vein Such catheters are very pliable and are readily manipulated centrally, the direction of blood flow guiding them In a few cases, radio-opaque material was injected down the venous catheter and a subsequent roentgenogram showed its distal end to be well placed in the right atrium or at the lower end of the superior vena cava Additional evidence of this fact was gained by the measurement of venous pressure through the catheter this pressure was invariably below 5 cm H_2O, a figure quite suggestive of its central location Samples of blood were removed at a steady rate over a period of 30 seconds each, in order to obtain a sample representative of the average cardiovascular dynamics during this particular minute while other measurements were being made Samples were at once analysed for pH, P_{CO_2} and P_{O_2} on an Epsco Medical Blood Parameters Analyser, Model 101, of the null detector type, working at a standard temperature of 37° C

Arterial systolic and diastolic pressures were stethacoustically monitored through a mercury Baumanometer Pulse rate and electrocardiogram were supervised with a Corbin Farnsworth Scopette

The cardiac output was determined by the carbon dioxide direct Fick technique, as described in our previous study This method, in our hands, yields reproducible results Values of cardiac output at rest, before and after anaesthesia, agree with accepted standards for patients of the age and sex of our patients Total peripheral resistance was calculated by dividing the mean arterial pressure by the cardiac output, as indicated by Aperia in his classic formula[6]

$$\frac{\text{mean arterial blood pressure}}{\text{cardiac output in c c /sec}} \times 1332 = \text{dynes/sec /cm}^{5}$$

Particular attention was paid to the obtaining of a steady state before any blood sampling was performed The presence of this state was appreciated by the similarity of several consecutive determinations of pulmonary ventilation, and by the stability of the CO_2 curve pattern as recorded from expired air

Some degree of sedation was found to be desirable before our patients were

submitted to this set-up Hence, they received, one hour before the operation, a moderate dose of meperidine along with atropine 0 4 mg Anaesthesia was induced by inhalation through the mask of a mixture of 2 litres of oxygen, 2 litres of nitrous oxide, and halothane-ether azeotrope in concentrations up to 5 per cent, depending on the patient's response No patient objected to this induction, which was smooth, never stormy, and free of any adverse reaction Sleep was produced very quickly, within 2 minutes, and operative conditions were obtained in 4 to 6 minutes Surgical anaesthesia was maintained with halothane-ether vaporized through a Vernitrol Vaporizer using a semi-closed system with 4 litres/min total gas flow and not less than 50 per cent oxygen mixed with nitrous oxide Stable maintenance, free of pain, reflexes, or overdosage, was obtained with concentrations of azeotrope fluctuating between 1 2 per cent and 2 5 per cent We should like to emphasize at this point that we have attempted to eliminate many factors which might interfere with the study of pharmacological actions of halothane-ether azeotropic mixture, such as the administration of a short-acting barbiturate at induction, endotracheal intubation, positive pressure in the airway either by assisted or controlled respiration, curares, solutes or blood transfusion Anaesthesia was kept at a moderate level, generally between the second and third planes of surgical stage III, as assessed by the absence of muscular movement in response to surgical stimulation, and by other standard Guedel criteria Respiration was left unassisted throughout

Results

Respiratory Effects

Table I shows the minute volume of ventilation, the rate of breathing, and CO_2 tensions in arterial blood before, during, and after halothane-ether anaesthesia Respiration before induction of anaesthesia was sometimes slightly depressed, likely owing to the premedication just received Maintenance during surgery, at the level of narcosis used, was attended by no respiratory depression The mean pulmonary ventilation before anaesthesia was 6465 c c , during surgery, 6877 c c ($P > 0\,05$), after surgery, it rose to 8400 c c This significant increase after surgery illustrates two properties of the azeotrope weak analgesia at emergence and virtual absence of respiratory depression in the recovery room In any case, P_{CO_2} remained well between 36 to 45 mm Hg, a range considered as normal by most laboratories With methoxyflurane, as we pointed out in our previous study, the pulmonary ventilation remained adequate for normal gas exchange in moderate levels of anaesthesia Most probably, the depressive effect of these two drugs was counteracted by stimuli from the operative site However, there is a clear-cut difference between respiratory patterns with these two agents With halothane-ether, there is a remarkable trend towards tachypnoea, a phenomenon well known with halothane alone, in our 9 patients, the rate rose from 19 to 27 per minute, a mean increase of 37 per cent ($P < 0\,02$) Hence it is possible that P_{CO_2} rises even if total pulmonary ventilation seems at first to be acceptable, alveolar hypoventilation being chiefly the result of an increase in

TABLE I

RESPIRATORY DATA PRECEDING AND ACCOMPANYING THE ADMINISTRATION OF HALOTHANE-ETHER TO 9 PATIENTS BREATHING SPONTANEOUSLY

Patient	Time (min)	Pulmonary ventilation (L/min)	Frequency	P_{CO_2} (mm Hg)	CO_2 output (c c/min)	Halothane-ether concentration (%)
1	−15	4640	13 7	40 1	185 6	
	15	5130	13 1	46 4	165 7	5
	30	6050	29 7	48 4	183 9	2 5
	60	8150	45 8	44 1	244 5	2 5
	90	6750	19 8	39 8	259 2	
2	−15	3700	24	47 6	95 9	
	20	4570	21 4	44 2	155 3	4
	45	5650	27 7	40 1	167 9	2
	60	6250	30 6	44 1	137 5	2 5
	105	4175	36 1	46 3	78 5	
3	−15	9600	20	30 5	288	
	30	7125	32	55 7	213 7	3
	60	10180	26	39 6	315 5	2 5
	75	6350	20	43 0	219	2
	110	7600	18	36 9	266	
4	−15	3050	22	37 5	93 5	
	20	5100	30	35 3	163 8	4
	45	4000	29 5	35 5	116 0	2 5
	90	6300	30	36 8	151 2	2
	120	6000	28	37 5	126	0 5
	150	6000	20	38 1	180	
5	−15	13450	20	38 2	484	
	25	8400	20 5	45 4	496 4	2 5
	60	11100	17 5	37 7	399	
6	−15	6353	24 4	40 1	206 7	
	40	6220	14	42 8	279 9	5
	60	6530	16 4	45 2	271 6	2
	75	6700	17	44 6	274 7	1 25
	120	8130	26	38 9	243 9	
7	−15	4700	13	39 3	194 6	
	15	7240	20	33 8	249 7	5
	30	8830	21	36 1	284 3	2 5
	90	9200	26	37 8	338 5	2 5
	105	8600	26	36 2	286 3	2 2
	120	9600	21	29 6	330	
8	−15	6050	20	40 7	229 9	
	30	5000	25	44 5	170	2 5
	45	9300	40	41 5	297 6	2 5
	90	9250	32	45 5	259	1 2
	120	10750	30	39 6	357 9	
9	−15	6650	21	35 8	242 7	
	30	6100	37	40 4	183	2
	60	7850	37	42 1	329 7	1 2
	90	5700	32	38 5	193 8	1 2
	120	6800	33	35 3	251	1
	180	8400	22	40 2	252	

dead volume ventilation With methoxyflurane, most observers agree that the respiratory rate progressively decreases during the course of anaesthesia, shallow bradypnoea always indicating very deep narcosis

CO_2 output may be used indirectly to appreciate the basal metabolic rate during anaesthesia There is a well-known relationship between cardiac output

and body metabolism [7,8] Therefore, it is reasonable to suspect that the administration of a drug which lowers O_2 consumption and CO_2 production could also be attended by a low cardiac output, and vice versa Methoxyflurane usually induced a significant depression of CO_2 production and elimination, from a mean of 240 c c before anaesthesia to a mean of 199 c c during anaesthesia The azeotrope, however, seems to cause a very slight increase in CO_2 output Before anaesthesia, the mean CO_2 output was 224 c c , during maintenance, 232 c c , a difference too small to be of statistical value ($P > 0.05$), but nevertheless indicative of a positive tendency Diethyl ether has been shown to produce hypermetabolism during anaesthesia, possibly owing to a release of epinephrine and central sympathetic stimulation [9,10]

Metabolic Effects

Figure 1 presents a summary of the relationship between P_{CO_2}, pH, and CO_2 content in the arterial blood of our 9 patients anaesthetized with the azeotrope

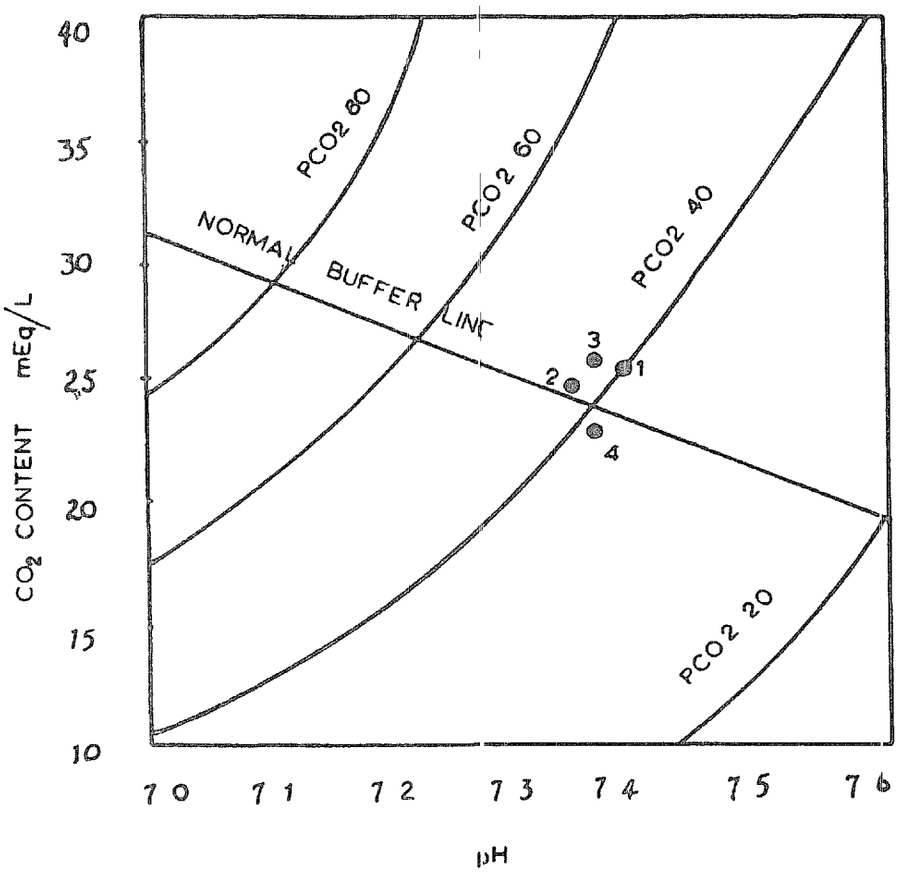

FIGURE 1 Effect of the halothane-ether azeotrope on acid-base balance in nine patients breathing spontaneously 1, before induction 2, during maintenance, 3, at the end of the operation, 4, after complete recovery (after Davenport[22])

This study suggests that no important variation in acid-base balance follows the administration of this agent Dobkin,[2] reporting on 10 cases in 1959, reached the same conclusion It is unlikely that the ether fraction of the azeotrope would induce the same metabolic acidosis as ether administered alone This is a question of dosage and concentration, during straight ether anaesthesia, a patient is

exposed to a concentration of about 4 per cent for maintenance, while with the azeotrope, for the same level of anaesthesia he will receive only 0 8 per cent ether vapour Hudon,[5] Dobkin,[11] and their collaborators reported a slight trend towards metabolic acidosis with methoxyflurane, this disturbance being, in their view, small and insignificant

An important metabolic effect of halothane-ether anaesthesia is a change in blood glucose during its administration Blood glucose was evaluated in 6 patients anaesthetized with the azeotrope alone, who received no dextrose perfusion during anaesthesia Figure 2 summarizes the experimental data found in these

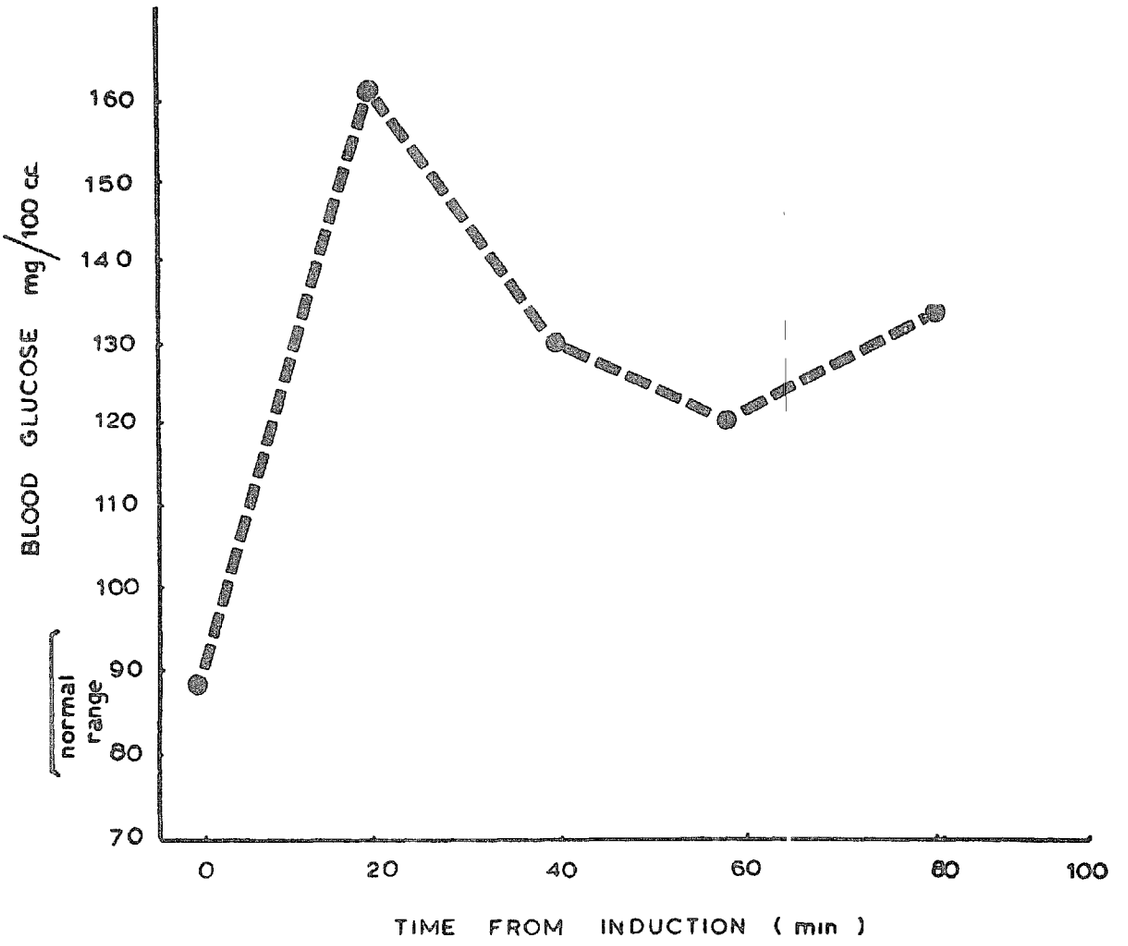

FIGURE 2 Mean blood glucose levels in five patients submitted to halothane-ether anaesthesia

patients Blood glucose increased significantly in every patient the mean value before anaesthesia was 0 88 gm ‰, the concentration after 20 minutes had almost doubled, to 1 61 gm ‰ (the significance of the difference being highly positive at the 5% level) Later on, mean blood glucose sustained an elevated plateau at 1 30 gm ‰ till the end of anaesthesia Blood glucose levels were not studied once these patients left the recovery room The reason why the azeotrope can produce hyperglycaemia, yet cannot induce a metabolic acidosis, is unknown at the present time It only suggests that ether acidosis may be unrelated to ether hyperglycaemia [10] However, this study clearly indicates that the halothane fraction does not block the hyperglycaemia induced by the ether fraction of the azeotrope

Cardiovascular Effects

Table II gives the major haemodynamic findings in each case

1 *Heart rate* This was always significantly decreased during halothane-ether anaesthesia Figure 3 illustrates this predominant effect One patient experienced nodal rythm, an arrhythmia which is commonplace with methoxyflurane, halothane, and even with ether

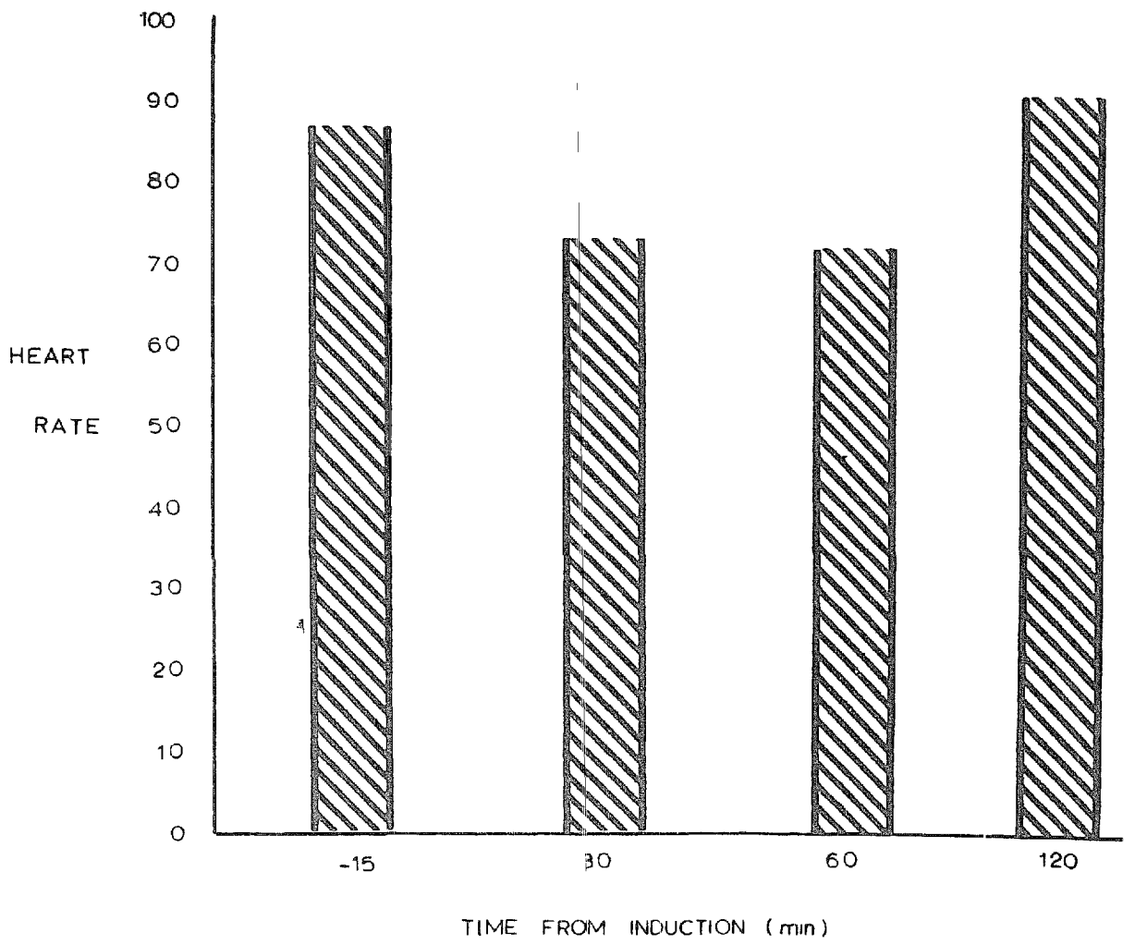

FIGURE 3 Average heart rates in nine patients anaesthetized with the halothane-ether azeotropic mixture

2 *Blood pressure* With the patients moderately anaesthetized with the azeotrope, the decrease in arterial systolic pressure was very slight—from a mean of 126 mm Hg before to 109 mm Hg during maintenance ($P < 0.01$) Diastolic pressure did not vary Postoperatively, the blood pressure remained at pre-anaesthetic levels in most of our patients Incidentally, this small disturbance in arterial blood pressure was very similar to the one we noticed during methoxyflurane anaesthesia

3 *Cardiac output* Although three groups of investigators have reported the occurrence of myocardial depression during halothane-ether anaesthesia, the data presented above demonstrate that in all our cases the administration of the azeotrope was followed by a sustained increase in cardiac output during surgery The cardiac output at rest for the 9 patients considered to be in a basal state averaged 4973 c c per minute Maintenance of anaesthesia was accompanied by

an increment in cardiac output to a mean of 6692 c c per minute, this 54 6 per cent increase, submitted to Student's t-test, proved to be significant at the 5 per cent level Only when overdosage was obtained and blood pressure reduced to marked hypotensive levels did the cardiac output decrease In no instance did cardiac output decrease after anaesthesia mean cardiac output at emergence was 5550 c c per minute, this slight increase being insignificant ($+11\%$, $P > 0\,05$) In four of these studies, the cardiac output did not rise appreciably immediately after induction, this is due to higher concentrations and deeper anaesthesia concomitant with the induction period

On the whole, this picture is quite different from what we observed in 20 normocapnic patients studied under comparable conditions during methoxyflurane anaesthesia From a mean cardiac output of 5549 c c per minute before induction, 75 per cent of those patients presented a 20 per cent decrease in their cardiac output during maintenance, and 60 per cent experienced a 38 per cent decrease in the recovery room

4 *Peripheral resistance* Vasodilatation is a peculiar feature of halothane-ether anaesthesia This statement should be easily accepted, it is substantiated by the fact that both ether and halothane have been reported to lower peripheral resistance Total peripheral resistance fell markedly and constantly in our 9 patients during maintenance with the azeotrope initially at 1836 dynes/sec cm^{-5}, it fell to 1215 dynes during maintenance (mean decrease 33%, $P < 0\,001$) In the recovery room, these patients still exhibited, although to a lower degree, some residual vasodilatation which accounted for their excellent colour their skin was pink, dry, and warm (mean resistance 1456 dynes/sec cm^{-5}) In order to confirm this vasodilatation during halothane-ether administration, cutaneous temperature was monitored with a Yellow Spring Thermistor thermometer in 5 patients during extrathoracic and extra-abdominal operations Very soon after induction, each patient showed a 3° F increase in skin temperature, this increase being sustained afterwards for the whole duration of anaesthesia Incidentally, this is the usual increase occurring after surgical or pharmacological sympathectomy Meanwhile, the central temperature changed very little This vasodilatation is conspicuous on the whole body skin surface, but is particularly well illustrated at the level of the vascular network of the bulbar conjunctiva Figure 4 gives pictures of the same eye before and during anaesthesia with the azeotrope They show an unquestionable increase in vascularity Micrometric measurements of these vessels beneath the microscope as they appear on colour slides disclosed a 45 per cent increase in the calibre of conjunctival vessels during anaesthesia

Methoxyflurane departs widely from these features Its administration has been shown to produce in most of our patients a significant increment in peripheral resistance, this vasoconstriction being related to the concomitant fall in cardiac output Figures 5 and 6 represent this vasoconstriction as manifested at the level of the bulbar conjunctiva before, during, and after anaesthesia with this drug

5 *Myocardial work* Left ventricular work against pressure was calculated as the product of mean brachial arterial pressure and cardiac output, and expressed in kilogram-metres per minute [12] The omission of kinetic energy in this calculation

TABLE II

OBSERVATIONS OF HAEMODYNAMICS AND RELATIVE DATA DURING HALOTHANE-ETHER ANAESTHESIA IN 9 PATIENTS

Subject, nature of operation, sex, age	Time (min)	Cardiac output (c c /min)	Arterial pressure (mm Hg)	Total periph resistance (dynes/sec)	Left ventricular work against pressure (kg /min)	Arterial blood CO_2 (vol %)	Venous blood CO_2 (vol %)	Arterial pH
1 L H, herniotomy and appendectomy, female, 21	−15	4419	95/70	1493	5 64	55 9	60 1	7 403
	15	7205	90/60	555	8 4	54 5	56 8	7 33
	30	4946	100/70	1374	6 5	57 3	61 0	7 339
	60	8431	90/60	612	9 89	52 2	55 1	7 332
	90*	4050	100/75	1726	5 1	53 4	59 8	7 394
2 L A limb female 76	−15	3309	100/60	1937	4 8	61 1	64 0	7 367
	20	5176	85/42	952	5 0	57 3	60 3	7 379
	45	8842	115/65	815	12 4	54 0	55 9	7 398
	60	4900	120/65	1513	7 0	57 1	59 9	7 375
	105*	3568	140/70	2370	5 8	62 1	64 3	7 392
3 M R, herniotomy, male, 32	−15	5760	140/90	1700	10 2	53 8	58 8	7 501
	30	4410	115/80	1896	6 4	62 0	67 2	7 31
	60	10519	115/80	742	16 4	63 0	66 0	7 469
	75	10429	105/70	673	14 1	63 0	65 1	7 382
	110*	6333	110/75	1167	9 1	48 5	52 7	7 382
4 C M, bone graft, female, 76	−15	3018	150/80	3064	5 42	63 8	67 0	7 497
	20	5610	125/75	1494	8 7	46 0	49 0	7 375
	45	3513	105/70	1988	4 5	44 0	47 3	7 349
	90	3516	95/70	1875	4 5	54 1	58 3	7 437
	120	5250	95/70	1256	6 6	51 5	53 9	7 418
	150*	4285	90/70	1522	5 4	55 3	59 5	7 421

5 L Ls P , bone, male, 35	−15	7934	120/85	1030	12 6	56 4	62 5	7 438
	25	8274	120/80	965	11 8	57 8	63 8	7 361
	60*	7390	95/50	699	9 5	53 2	58 6	7 415
6 H R , stripping, female, 46	−15	3691	160/95	2750	7 7	52 2	57 8	7 371
	40	8232	130/90	1011	15 2	53 8	57 2	7 346
	60	9053	108/86	861	13 6	58 4	61 4	7 374
	75	5972	130/90	1465	10 1	60 0	64 6	7 39
	120*	6968	120/78	1137	10 8	53 5	57 0	7 40
7 F G , herniotomy, female, 63	−15	5723	138/80	1528	9 76	55 0	58 4	7 405
	15	5550	100/70	1230	7 3	42 8	47 3	7 360
	30	8123	105/75	888	11 4	46 6	50 0	7 369
	90	9404	128/88	913	15 6	44 0	47 6	7 321
	105	6508	120/80	1233	10 1	44 9	49 3	7 350
	120*	6735	130/90	1300	11 5	42 0	46 9	7 401
8 L N , stripping, female, 23	−15	6050	120/75	1376	9 24	59 2	62 8	7 421
	30	3700	115/80	2108	5 7	57 5	62 1	7 374
	45	6921	115/85	1146	10 86	55 6	59 9	7 390
	90	8100	115/80	962	9 62	58 8	62 0	7 371
	120*	6280	125/80	1276	9 96	54 5	60 2	7 409
9 C P , stripping, female, 35	−15	4854	115/85	1646	7 6	46 0	51 0	7 364
	30	4060	104/80	1812	5 8	59 1	63 6	7 425
	60	8454	110/80	898	12 56	53 8	57 7	7 366
	90	5876	106/80	1306	8 62	47 3	50 6	7 346
	120	6972	108/80	1077	10 2	51 4	55 0	7 421
	180*	4345	112/95	1904	6 88	47 1	52 9	7 322

*These represent data collected after the end of anaesthesia

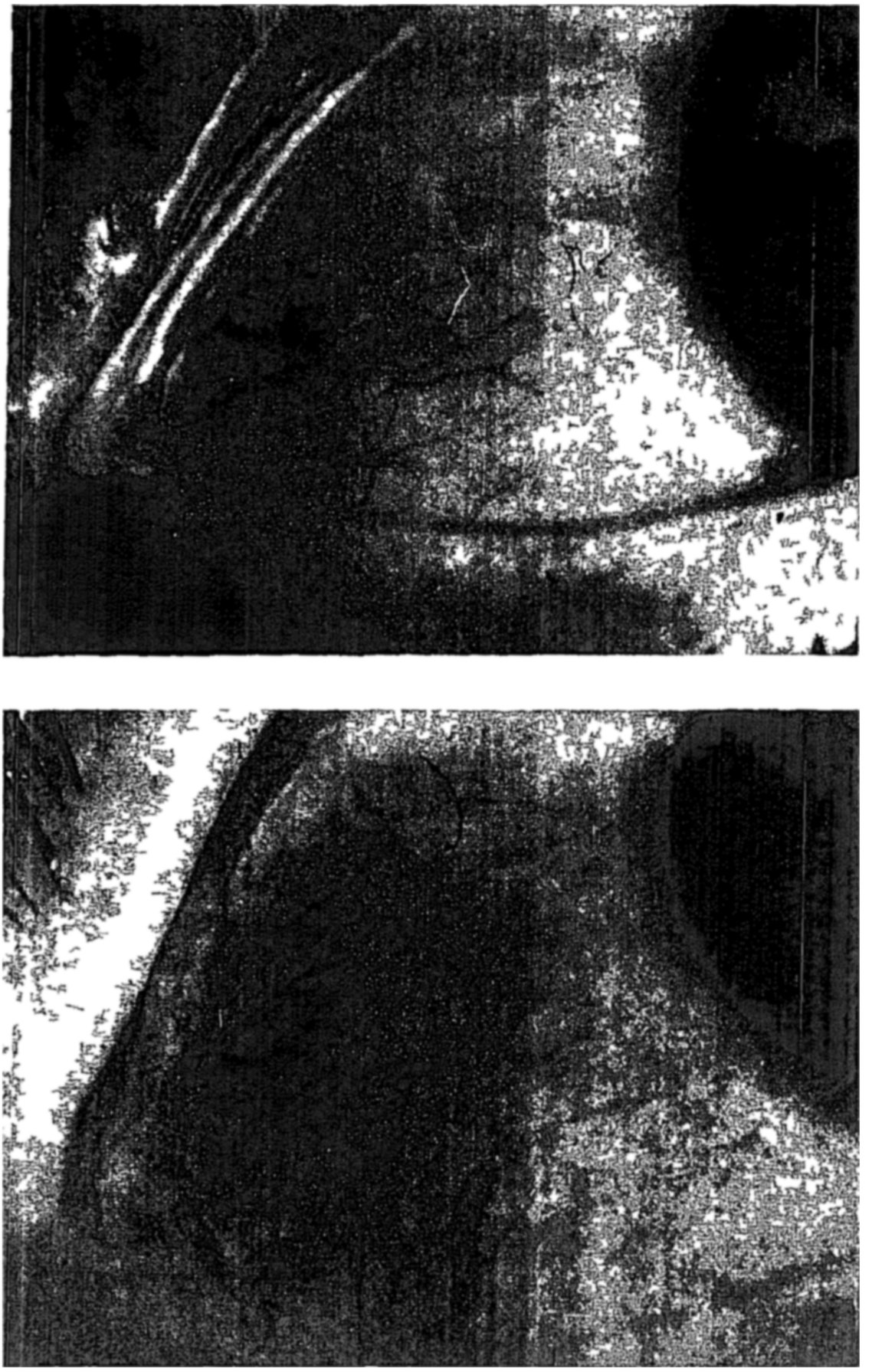

FIGURE 4 Aspect of the onj n t val ıs lar n t ork befor (top) and d ng (bott m) halotha ethe anae the a (M gn fi at on 5 3)

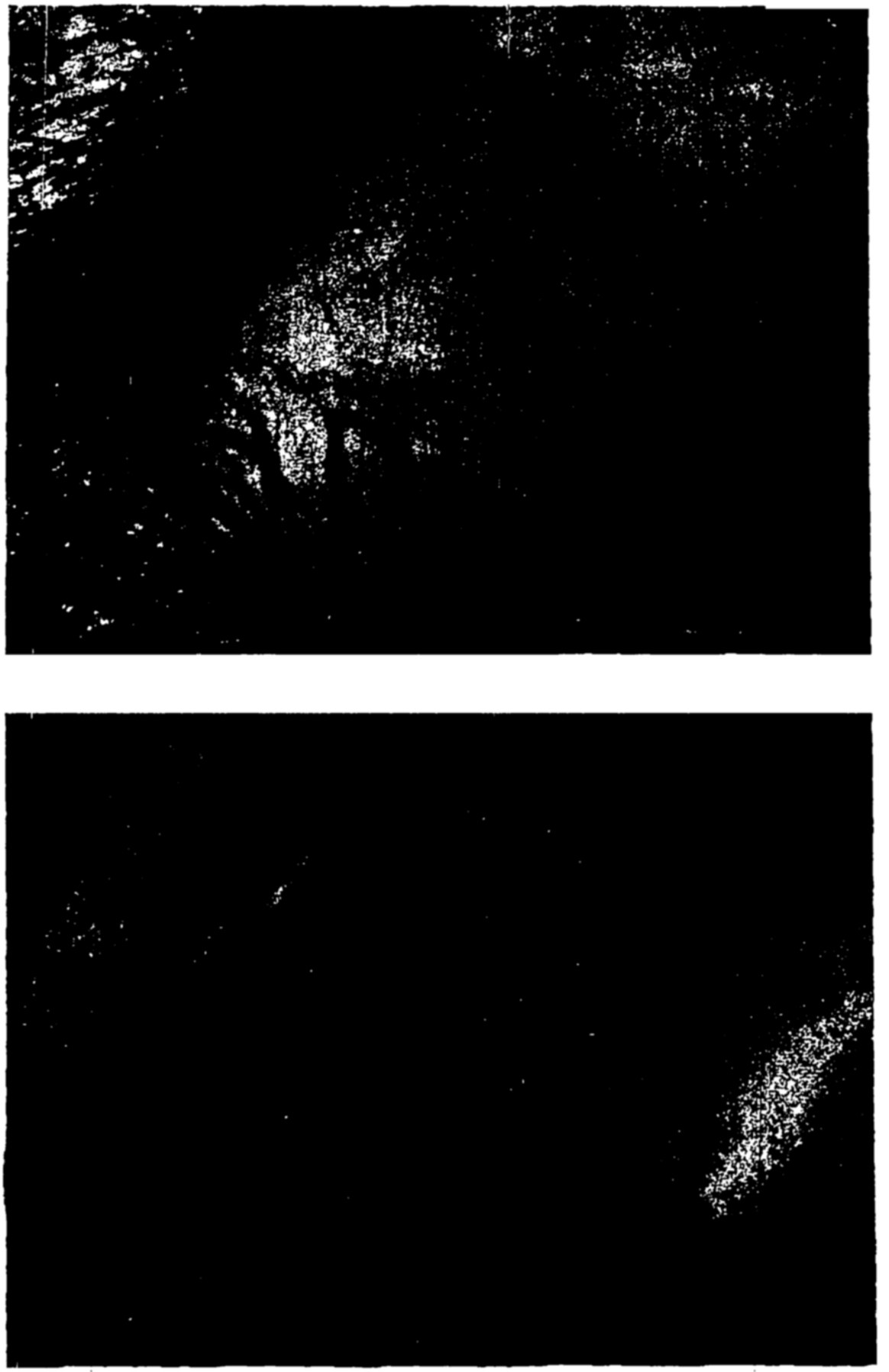

FIGURE 5 Aspect of the bulbar conjunctiva before (top) and during (bottom) methoxy flurane anaesthesia (Magnification 5 3)

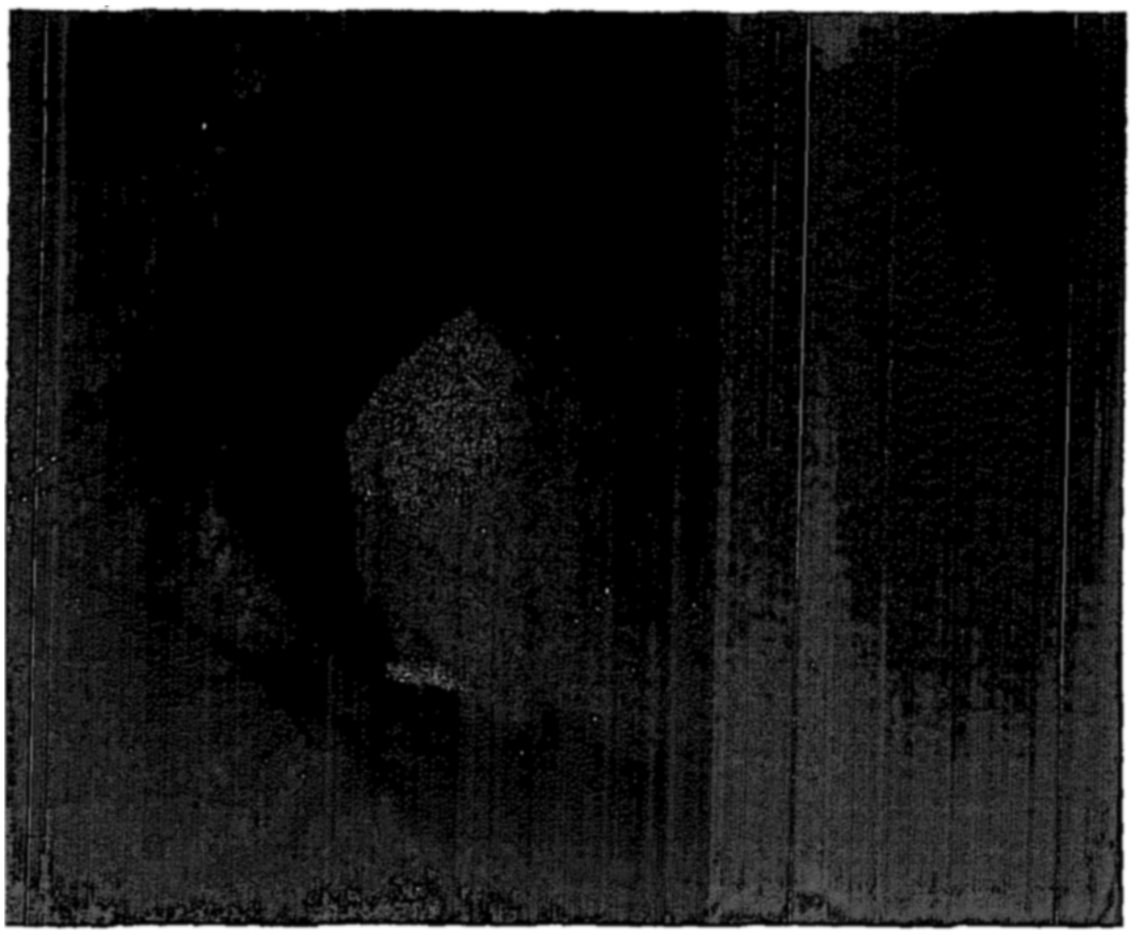

FIGURE 6 Aspect of the bulbar conjunctiva after methoxyflurane anaesthesia (Magnification 5 3)

ordinarily introduces no serious quantitative error During halothane ether anaesthesia myocardial work against pressure as shown from data in Table II was not decreased proportionally to the decrease in peripheral resistance load thus suggesting that even if vasodilatation was beneficial to the heart in the sense of efficiency the inotropic activity of the heart was further enhanced by some hormonal humoral or reflexogenic mechanism

DISCUSSION

We shall now try to give tentative explanations of our results The data presented above suggest that when a moderate dosage of the halothane ether azeotropic mixture was administered to patients two major dynamic alterations were induced vasodilatation and increase of cardiac output Clinical experience leaves little doubt in our minds that both effects occur and are of significance

The ability of halothane to cause vasodilatation and to block effectively the excitatory effects of catecholamines on blood vessels has been repeatedly noted There also exists some evidence of inhibition of the adrenal medulla during its administration However as reported by Burn[13] and Millar and Morris[14] this blockade is rather incomplete at the level of ganglia and synapses and most probably does not inhibit the release of the adrenergic transmitter in response to adrenergic nerve stimulation This partial blockade seemingly takes place in the vascular wall itself[15 16 17] on alpha adrenergic receptors through a mechanism of inhibition or competition This inference gains additional confirmation from

the fact that vasopressors which act specifically on alpha receptors command a poorer response during halothane anaesthesia, so it is possible that the rather impressive vasodilatation seen during halothane-ether anaesthesia might be due to the effective inhibition of neurogenic tone by direct action of the halothane fraction on vessels

On the other hand, halothane-ether seems to afford some protection to the heart itself This seems logical if one remembers that cardiac muscle and the coronary vascular bed are essentially lacking in alpha receptors [18] Adrenergic blocking agents, which readily block alpha receptors, have been shown to have no direct effect on the heart itself Nickerson[19] reports in his review of the question that none of a wide variety of natural and synthetic agents which effectively block the excitatory effects of epinephrine in smooth muscle is capable of giving a clear-cut blockade of its excitatory effects in mammalian heart Goodman and Gilman[20] are in complete agreement with this statement In their view, adrenergic stimulation of the heart is yet possible after adrenergic blockade So the heart during light and moderate halothane anaesthesia is potentially able to answer adrenergic stimulation This is where the ether fraction of halothane-ether comes in Ether has been shown to improve ventricular function and cardiac efficiency by its stimulating action on sympathetic centres Whether this stimulation is neurogenic or humoral or both at the same moment is yet unknown One fact remains experiments designed to demonstrate that ether administration reduced the contractile force of the heart were performed either on isolated mammalian hearts or in sympathectomized individuals But during clinical halothane-ether anaesthesia, the sympathetic nervous tracts leading to the heart remain relatively unaltered, and seemingly able to fire at a high rate The increase in cardiac output we noted in our patients is strong presumptive evidence that this drug had, either by its direct action on the heart or by an indirect action through sympathetic stimulation, improved ventricular function and enhanced cardiac efficiency as a whole

One need not fear sympathetic activity during anaesthesia In our opinion, every anaesthetic agent currently in use leaves some degree of wakefulness to the sympathetic system One can praise an anaesthetic drug whose administration weakens sympathetic centres, interrupts adrenergic reflexes at the level of the ganglia, isolates the adrenal medulla, and even abolishes receptor response, till the day when one is faced with the overwhelming dilemma of providing anaesthesia to a patient whose catecholamine stores have been depleted and adrenergic system really dampened, let us say by previous reserpine treatment Then one realizes how important these sympathetic nervous reactions are in terms of survival and response to acute stress

We have shown that methoxyflurane protects this sympathetic reactivity, but theorically through some threat to peripheral perfusion When methoxyflurane anaesthesia is prolonged or deep, direct myocardial depression is readily compensated by intense vasoconstriction of the peripheral vascular bed, which is readily appreciated clinically by the pallor of the skin, decreased tegumental temperature, cyanosis of nailbeds and mucous membranes The halothane-ether azeotropic mixture departs from these features if, on the one hand, its halothane

fraction induces sustained vasodilatation, its ether fraction, on the other hand, compensates by enhancing strength of cardiac contraction, cardiac efficiency, and output Thus, ideal conditions are set up for visceral perfusion According to hydraulic principles, it is far more logical, in order to maintain ideal visceral perfusion, to dilate the peripheral vascular bed while stimulating the pump, than either to constrict the periphery after having depressed the pump, or to depress both vascular tone and myocardial action Far from being illogical[21] the azeotrope proves to be a pharmacologically sound, balanced association, one component correcting some deficiency of the other

Finally, it must be recognized that with very deep anaesthesia, with the azeotrope, the heart is weakened by direct action of the drug on the myocardium itself If we combine (*a*) the beneficial effect of decreased peripheral resistance on the heart, (*b*) the effect of sympathetic reflex stimulation, and (*c*) the direct weakening action of halothane-ether on the heart, we come to the conclusion that, in light to moderate planes of anaesthesia, the first two factors predominate, with a deepening level of narcosis, the three factors may well cancel out, with very deep anaesthesia, cardiac output is diminished to an extremely low level [1]

Summary and Conclusion

The administration of halothane-ether azeotropic mixture to the surgical patients included in this study produced no respiratory depression, no acid-base disturbances, a clear-cut hyperglycaemia, bradycardia, a definite reduction in peripheral resistance, and an elevated cardiac output The above observations suggest an absence of significant myocardial depression with the azeotrope when used in normal clinical concentrations A sustained increase in myocardial efficiency is produced, which might be beneficial in terms of visceral perfusion In our opinion, cardiac sympathetic nerves and beta receptors are not blocked by the halothane fraction, their activation by the ether fraction being a major factor of safety for the heart Mutual corrective effects of these two fractions result in a sound, balanced anaesthetic state

So far halothane-ether and methoxyflurane have been shown to differ in many respects In the future, it will be possible to stress with more precision the indications for each For the time being, what we appreciate most in methoxyflurane is its wide margin of safety and the remarkable stability it gives to haemodynamics during maintenance What we appreciate most in the azeotrope is its flexibility (at the price, it is true, of a somewhat narrower margin of safety) and the preservation of a warm, pink, and dry patient who, to the satisfaction of all concerned, will fall asleep quickly and will rapidly awaken from sleep *

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