CIRCULATORY CHANGES ASSOCIATED WITH THIOPENTAL ANESTHESIA IN MAN * † ‡

J. D. Elder, Jr., M.D., S. M. Nagano, M.D., D. W. Eastwood, M.D., and D. Harnagel, M.D.

St Louis, Missouri

Previous studies (1) on the circulatory response to increased airway pressure under thiopental anesthesia indicate on the basis of intra-arterial pressure that changes were present which greatly modified the vasomotor response to this stress. Other investigations (2), which include determination of blood flow, have been made on combinations of anesthetic agents and during surgical operations. It is the purpose of the authors of the present study to extend the measurements upon the changes which occur in the early stages of barbiturate anesthesia by determination of the cardiac output. These changes have been studied without the complication of surgical stimulation, hemorrhage, or the loss of fluid into traumatized tissue in order that all the observations can fairly be attributed to anesthesia.

Method

A total of 62 cardiac output determinations have been made on 15 hospital patients. One of these was given curare before any determination could be made under thiopental, and therefore is not included. The patients in this series were selected from those scheduled for barbiturate anesthesia with only the consideration of available time and the ability of the investigators to obtain the desired determinations.

Under local anesthesia, procaine 1 per cent, a needle was introduced into the brachial artery where its patency was maintained throughout the study by means of a heparinized manifold. A fine catheter (plastic continuous spinal) was introduced through an 18 gauge thin-wall needle and threaded up into the central venous system with the tip well inside the thorax. No exact localization was attempted, but in all instances both respiratory variations and the typical central venous pulsations were sought. In 3 cases, central venous pressure was recorded through this catheter and these pressures are referred to the second costochondral junction.

* From the Division of Anesthesiology, Washington University School of Medicine, St. Louis, Missouri.

† Read before the meeting of the Southern Society of Anesthesiologists, Miami Beach, Florida, April 23, 1954.

‡ Accepted for publication July 19, 1954.

Mean arterial blood pressure was obtained through the indwelling arterial needle by means of a damped mercury manometer.

Cardiac output determinations were made by a modification of the technique of Bing (3), using T 1824 (Evans blue) dye.‡ In 10 instances, calibrations were done for the effect of T 1824 dye in the blood of the individual. Since these calibrations all fall within ± 7 per cent of their mean, it was not felt that a great error would be introduced in using the average value in those patients where such determinations were not available.

The patients were premedicated with 8 to 10 mg. of morphine and either 0.4 mg. of atropine or scopolamine in dosage of 0.3 or 0.4 mg. In most instances, the premedication was given over 1 hour before the control determinations. In 3 cases it was necesary to give the premedication intravenously in order that the effect might be relatively stable during the period of observation. The intravenous administration was made 20 to 30 minutes prior to the control observations.

Since the primary purpose of the authors in this study was to determine the effects on man of clinical barbiturate anesthesia, the patients were given nitrous oxide with oxygen during the determinations on thiopental. Oxygen percentages with high flows were maintained between 30 and 50 per cent. While the presence of nitrous oxide may modify the findings, this agent is or should be used with almost all barbiturate anesthesia. The results, therefore, are in keeping with the usual clinical use of thiopental anesthesia.

RESULTS

Cardiac Index (Cardiac Output in L./min. divided by surface area)

The cardiac indices show a fall in 12 cases (86 per cent), a rise in 1 case (7 per cent), and in 1 case there was no change between the pre-anesthetic sedated determination and that done after the induction of anesthesia.

The average cardiac index during the sedated control period was 4.79 L./min./m.^{2} (range 2.93 to 7.91) in 8 males and 4.82 L./min./m.^{2} (range 4.37 to 5.49) in 6 females. The average after induction in 8 males was 3.80 L./min./m.^{2} (range 2.36 to 5.38) and 3.70 L./min./m.^{2} (range 3.04 to 4.83) in the females.

Among those who showed a decrease in cardiac index, the average during anesthesia was 3.58 L./min./m.^{2} (range 2.36 to 5.36) in 6 males,

‡ Accuracy of the method: in order to establish if possible the accuracy and the reproducability of blue dye curves, duplicate determinations have been made in all patients during the control period. Comparison of these duplicate determinations yields a mean which is exactly the same in both instances. The standard deviations differ between the sets of determinations by only 3 per cent of the mean determined value.

If the paired determinations are compared in groups, it also can be seen that 70 per cent of the repeat determinations differ by less than 10 per cent and none differs by more than 18 per cent.

and 3.70 L./min./m.^{2} (range 3.04 to 4.83) in 6 females. This represents a 24 per cent fall in cardiac index of the pre-anesthetic value for males and a 23 per cent fall for females. The single man who showed a rise in cardiac index with induction of anesthesia had a cardiac index of 4.39 L./min./m.^{2} during anesthesia, an increase of 3 per cent over the pre-anesthetic value.

Blood Pressure

The mean arterial pressure showed a fall in 5 males and in all 6 female subjects. A rise of 2mm. of mercury was present in 1 male and the blood pressure remained unchanged in 2 males. Among the 5 males who showed a fall, there was an average decrease of 8 mm. of mercury (9 per cent of the pre-anesthetic value), while the 6 females showed an average decrease of 22 mm. of mercury in mean blood pressure (26 per cent of the pre-anesthetic value).

Venous Pressure

Both peripheral and central venous pressures have been measured during this study. In 1 male (case 10), who showed no change in cardiac index, there was a rise of 6 mm. saline in peripheral venous pressure. The remaining cases, both male and female, showed a variable amount of fall in venous pressure regardless of the point of measurement. The average decline among those who fell amounts to 15 per cent of the initial determination.

Total Peripheral Resistance

The over-all resistance to the outflow of blood from the arterial tree has been calculated according to the formula of Apiera (4) to obtain:

$R = P/F \times 1332 \times 60$ in dyne-cm./sec., where P = mean arterial blood pressure and F = output per minute. The values so calculated showed the widest scatter of all determinations. Six male patients showed a rise in resistance, an average of 21 per cent, on induction of anesthesia, and 2 males showed a fall of 21 per cent and 15 per cent, respectively. Taking all the males together, there was an average rise of 10 per cent. The 6 females are divided evenly, 3 showing a rise of 15 per cent in over-all resistance, and 3 showing a decrease of 19 per cent. The average for all females in this series yields a fall in resistance of 2 per cent.

It should be observed that the patients who showed a fall had an initial value which was usually high, while those who showed an increase had low initial values.

When the entire series was grouped according to the shift in over-all resistance, the highest determined average was the pre-anesthetic value

for those who showed a fall with induction of anesthesia. The lowest average value was found for those showing a rise under anesthesia. Both of these groups had values between these extremes while under anesthesia.

A plot of changes of total peripheral resistance against changes in output (fig. 1) showed a very wide variation, but in general there was a rise in over-all resistance rather than a fall with decreasing cardiac output. This finding was borne out by the averages for all cases, which showed a rise in over-all resistance for our series.

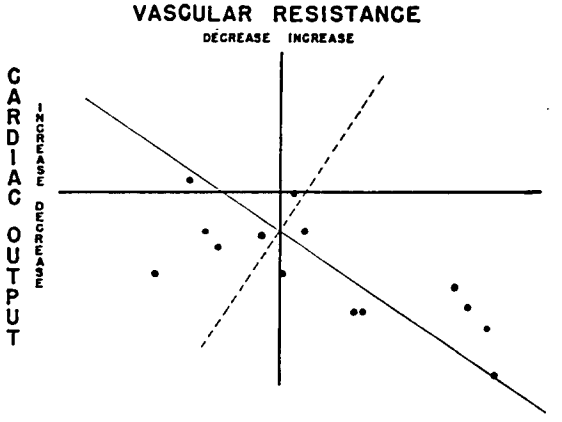

FIG. 1. Change in vascular resistance plotted against changes in cardiac output. The dotted line represents the expected directional change with ganglionic blockade.

Since average values of small series, particularly for such variable physiological determinations as cardiac indices, may be inaccurate or misleading, the individual determinations are included in table 1.

DISCUSSION

The average value of the cardiac index for the patients in this series during the pre-anesthetic period was somewhat higher than the value reported by Cournand *et al.* (5) for normal males. However, it was somewhat lower than previously reported preoperative values (2).

The possibility that this pre-anesthetic index was elevated due to apprehension and that the observed fall on induction was only the result of "sedation" to a basal output must be considered. If the high pre-anesthetic value were due to emotional disturbance alone, an in-

TABLE 1

CIRCULATORY CHANGES ASSOCIATED WITH THIOPENTAL ANESTHESIA IN MAN

	Case	Pre-induction (Sedated)				Post-induction (Thiopental)				
		Cardiac Index, L./min./m.²	Mean Arterial Pressure, mm.Hg	Venous Pressure, mm. Saline	Total Peripheral Resistance, Dyne-cm./sec.	Cardiac Index, L./min./m.²	Mean Arterial Pressure, mm.Hg	Venous Pressure, mm. Saline	Total Peripheral Resistance, Dyne-cm./sec.	Per Cent Change in Cardiac Index
Males	1	5.55	111		51,300	4.00	93		59,400	−28
	2	7.91	101		31,400	5.38	100		46,900	−32
	4	4.25	112	70	71,400	4.39	91	59	56,100	− 3
	5	3.42	62	100	47,400	2.36	62	85	68,800	−27
	8	2.93	53	50	51,000	2.68	52	35	54,200	− 9
	10	5.11	65	150	35,800	5.11	67	156	36,900	0
	13	4.45	80	40	39,300	3.45	80	30	56,200	−22
	14	4.16	101	15	62,900	3.62	75	5	53,300	−13
Average, all males		4.72	86		48,800	3.87	78		54,000	
Females	3	5.40	89		42,100	4.83	77		40,600	−10
	6	5.49	66	155	33,900	3.04	56		51,600	−45
	9	4.85	80	40	54,200	3.53	70	25	65,100	−27
	11	4.42	106		60,400	3.26	74		60,700	−26
	12	4.37	74	22	5,700	3.53	42	20	40,400	−19
	15	4.42	101	15	61,800	4.02	75		50,400	− 9
Average, all females		4.82	86		52,600	3.70	66		51,500	

crease in over-all vascular resistance might be anticipated, but such a situation would lead to extreme elevations in blood pressure—that is, increased flow plus increased resistance. Such elevations were not present in our series. Should this high initial cardiac index be due to cardiac stimulation with compensating vasodilatation through the carotid sinus control of blood pressure, the expected change upon release of excitation would be one of decreasing cardiac output with a compensating rise in over-all resistance so that the arterial pressure would show little change. The finding of a moderate decrease in mean arterial pressure in such a very high percentage of our studies indicates strongly that there is more depression of the cardiac output than can be explained on the basis of reduced excitement.

The occurrence of severe hypotension which occasionally is seen in the clinical use of barbiturate anesthesia has been interpreted as sympathetic blockade. In addition, evidence obtained during the course of studies on respirations (6) conducted on animals under barbiturate anesthesia have been interpreted as showing a response very similar to that seen with ganglionic blocking agents.

The circulatory response of man to positive pressure inflation of the lungs (1) bears out the animal experiments well in that severe

hypotension is produced with pressures of 12 to 20 cm. H_2O. This hypotension shows less tendency to return toward normal under thiopental anesthesia than in the pre-anesthetic period. There is also some diminution of the "overshoot" after the release of the airway pressure under anesthesia as compared with control determinations. Both these reactions are attributed to the reflex vasoconstriction (7–9) which is present in the conscious state and the decrease in these responses after thiopental is assumed to be due to a relative failure of the vasomotor response. Additional evidence has been added for a decrease in peripheral resistance under deep thiopental anesthesia (10) from the depression of the dicrotic notch in pulse-pressure curves.

The circulatory response in this series, recorded in table 1, does not indicate that thiopental produces a marked depression of the vasomotor mechanism as presented in the foregoing paragraphs. Only in those cases which show a high over-all resistance prior to induction is there a fall in resistance with thiopental. Most cases show a rise in total peripheral resistance with the decrease in cardiac output. While this rise is not entirely adequate, it represents in all probability the attempt on the part of a depressed nervous system to maintain blood pressure through the usual pressor receptor reflex pathways. Patients receiving ganglionic blocking agent would be expected to fall along the dotted line in figure 1, whereas our series corresponds much more nearly to the solid line which represents almost complete vascular compensation for a decrease in cardiac output.

The decrease in cardiac output which we have observed with thiopental must be due either to a direct depressant effect of the drug on the heart or to venous pooling with the observed decrease in cardiac filling pressure. The relationship between venous pressure and output was reasonably well maintained in this series. However, it can be seen from observation of the directional changes alone that the cardiac work (pressure x volume) was greatly reduced. It cannot be determined in the absence of any reliable method of obtaining quantitative estimates of the relation between cardiac work and filling pressure (11) whether pooling, if present, could cause the observed fall in output through the reduction of venous pressure alone. The other possibility that the observations are due to direct cardiac depression cannot be dismissed at present.

SUMMARY

An average fall in cardiac index of 20 per cent has been demonstrated in patients on induction of thiopental-nitrous oxide anesthesia. In addition, decreases have been found in mean arterial and venous pressure measurement.

The possible mechanisms of those circulatory adjustments have been discussed.

REFERENCES

1. Price, H. L.; Conner, E. H.; Elder, J. D., and Dripps, R. D.: Effect of Sodium Thiopental on Circulatory Response to Positive Pressure Inflation of Lung, J. Appl. Physiol. **4**: 629 (Feb.) 1952.
2. Shackman, R.; Graber, G. I., and Melrose, D. G.: The Haemodynamics of Surgical Patient Under General Anesthesia, Brit. J. Surg. **40**: 13, 1952.
3. Friedlich, A.; Heimbecker, R. O., and Bing, R. J.: Device for Continuous Recording of Concentration of Evans Blue Dye in Whole Blood and Its Application to Determination of Cardiac Output, J. Appl. Physiol. **3**: 12 (July) 1950.
4. Apiera, A.: Hemodynamical Studies, Skandinav. Arch. Physiol. Supp. **16**, 1940.
5. Cournand, A.; Breed, E. S.; Baldwin, E. D. F., and Richards, D. W.: Measurement of Cardiac Output in Man Using Techniques of Catheterization of Right Auricle or Ventricle, J. Clin. Invest. **24**: 106, 1945.
6. Maloney, J. V., Jr.; Affelatt, J. E.; Sarnoff, S. J., and Whittenberger, J. D.: Electrophrenic Respiration, Surg., Gynec. & Obst. **92**: 675, 1951.
7. Fenn, W. O., and Chadwick, L. E.; Effect of Pressure Breathing on Blood Flow through Finger, Am. J. Physiol. **151**: 270 (Dec.) 1947.
8. DeLalla, V. J.: Causes of Skin Cooling in Pressure Breathing, Am. J. Physiol. **152**: 122 (Jan.) 1948.
9. Hyman, C., and Dury, D. R.: Change in Pulse Velocity During Increased Intrathoracic Pressure, Am. J. Med. **8**: 538, 1950.
10. Howland, W. S., and Pepper, E. M.: Circulatory Changes During Anesthesia for Neurosurgical Operations, Anesthesiology **13**: 343 (July) 1952.
11. Ferguson, T. B.; Shandle, O. W., and Gregg, D. E.: Effect of Blood and Saline Infusion on Ventricular End Diastolic Pressure, Stroke Volume and Cardiac Output in the Open and Closed Chest Dog, Circulation Res. **1**: 62, 1953.