The Systemic and Coronary Hemodynamics of Tromethamine (THAM) in the Anesthetized Dog

George G. Rowe, M.D., Skoda Afonso, M.D., Jorge E. Lugo, M.D., Charles W. Crumpton, M.D.

The systemic and coronary hemodynamic effects of intravenous administration of Tromethamine (THAM) has been studied in intact anesthetized mongrel dogs. When approximately 750 mg./kg. of THAM was administered during a period of approximately 50 minutes blood *p*H was elevated from 7.26 to 7.42. In spite of this increase in blood *p*H significant changes did not occur in cardiac output, cardiac work, total peripheral resistance, coronary vascular resistance, or coronary blood flow. The cardiac rate and myocardial oxygen consumption increased significantly, whereas cardiac efficiency was reduced. These changes may well be nonspecific due to the hypertonicity or other characteristics of the THAM solution. There may be some support for nonspecific effect in the fact that the hemoglobin and hematocrit decreased suggesting hemodilution.

SINCE 1881 when Gaskell investigated the effects of *p*H on the isolated frog heart[1] there has been considerable interest in the hemodynamic effects of shifts in *p*H. The consensus derived from nonintact animal preparations and in the open chest dog indicates that cardiac performance is depressed in the low *p*H ranges and augmented as *p*H rises.[2-5] Furthermore, as *p*H rises, both epinephrine[6] and norepinephrine[2] are more effective in increasing the "contractile force" of the heart as measured by the strain gauge arch technique.

It appeared that since intravenous administration of tromethamine (tris (hydroxymethyl) aminomethane, THAM), has been shown to increase the blood *p*H,[7-10] it would be worthwhile to investigate the hemodynamic effects of this agent in intact anesthetized animals known to have low *p*H, apparently at least partially as a result of reduced ventilation. This seems particularly important since there is a strong tendency to transfer conclusions from the nonintact to the intact preparation, and since changes in the parameters measured in the previous studies may not produce significant hemodynamic effects. Furthermore, a recent review of the pharmacology of THAM[11] does not indicate that information is available concerning its systemic and coronary hemodynamic effects in the intact animal.

Material and Methods

The systemic and coronary hemodynamic effects of THAM were investigated in 13 intact mongrel dogs varying in weight between 13 and 27 kg. and averaging 21.4 kg. They were anesthetized with 3 mg./kg. of morphine sulfate injected subcutaneously, followed 1 hour later by 0.25 ml./kg. of a 50/50 mixture of pentobarbital and Dial-urethane.* After anesthesia was obtained, cardiac catheters were maneuvered fluroscopically into the pulmonary artery, right atrium, and coronary sinus and a Cournand needle was placed percutaneously in the femoral artery. Cardiac output was determined by the Fick principle with air collected in a Tissot spirometer via a cuffed endotracheal tube. Respiratory dead space was kept at a minimum by use of a short endotracheal tube inserted so that a Kirchhof nonrebreathing respiratory valve was placed well down into the opened mouth of the dog. This insures that the respiratory dead space is approximately equivalent to that of the dog when breathing normally through its nose. Analyses were done for oxygen and carbon dioxide in the blood specimens by the Van Slyke-Neill method[12] whereas expired air was analyzed by the method of Scholander.[13] Nitrous oxide determinations on the blood

Received from the Cardiopulmonary Research Laboratory, Department of Medicine, University of Wisconsin Medical School, Madison, Wisconsin; accepted for publication February 5, 1964. Dr. Rowe is Associate Professor of Medicine; Dr. Afonso, Research Associate in Medicine; Dr. Lugo, Research Fellow in Medicine; and Dr. Crumpton, Professor of Medicine and Director of the Laboratory.

* Dial-urethane contains Dial (di-allyl barbituric acid) 100 mg./ml., monethyl urea 400 mg./ml., and urethane 400 mg./ml. Veterinary pentobarbital contains 60 mg./ml. of pentobarbital.

TABLE 1. Hemodynamic Effects of THAM

Parameter	Control	Study	Δ* S.E.M.	P Value
Heart rate (beats/minute)	78	90	5.329	<0.05
Mean arterial blood pressure (mm. Hg)	107	111	2.305	<0.2
Mean pulmonary arterial blood pressure (mm. Hg)	12	11	0.416	<0.05
Mean right atrial blood pressure (mm. Hg)	3.5	2.8	0.247	<0.02
Minute volume of respiration (l./minute)	2.3	2.1	0.095	<0.1
Oxygen consumption (ml./minute)	110	111	1.542	<0.6
Carbon dioxide excretion (ml./minute)	95	72	1.959	<0.001
Arterial oxygen content (ml./100 ml. of blood)	16.7	15.1	0.311	<0.001
Arterial-venous oxygen difference (ml./100 ml. of blood)	4.0	3.9	0.251	<0.5
Venous carbon dioxide content (ml./100 ml. of blood)	52.6	64.6	0.446	<0.001
Venous-arterial carbon dioxide difference (ml./100 ml. of blood)	3.1	2.1	0.274	<0.01
Coronary sinus oxygen content (ml./100 ml. of blood)	5.6	3.5	0.450	<0.001
Arterial-coronary sinus oxygen difference (ml./100 ml. of blood)	10.9	11.9	0.457	<0.1
Coronary sinus carbon dioxide content (ml./100 ml. of blood)	57.3	72.7	0.924	<0.001
Arterial hematocrit (%)	40	37	0.747	<0.01
Arterial hemoglobin (g./100 ml.)	14.0	13.3	0.206	<0.02
Femoral arterial *p*H (units)	7.26	7.42	0.018	<0.001
Cardiac output (l./minute)	2.9	2.9	—	—
Left ventricular work (kg. m./minute)	4.1	4.4	0.268	<0.5
Right ventricular work (kg. m./minute)	0.5	0.4	0.032	>0.9
Total peripheral resistance (c.g.s. units)	3,343	3,283	249.4	<0.9
Total pulmonary resistance (c.g.s. units)	363	309	23.151	<0.05
Coronary blood flow (ml./100 g./minute)	88	98	6.909	<0.2
Coronary vascular resistance (units)	1.38	1.22	0.123	<0.3
Left ventricular oxygen usage (ml./100 g./minute)	9.2	11.5	0.734	<0.01
Index of efficiency (LVW ÷ LV O_2 usage)	0.46	0.39	0.028	<0.05

* Standard error of the mean difference.

specimens were done by the method of Orcutt and Waters.[14] Coronary blood flow was determined by the nitrous oxide saturation technique utilizing the partition coefficient of 1.0 between blood and myocardium. Pressures in the pulmonary artery, right atrium and systemic artery were recorded via Statham strain gauge pressure transducers and the means were determined by electrical damping on the Gilson macropolygraph. Standard formulae were used for all calculations.[15] In calculating cardiac work neither right nor left atrial pressure were subtracted from the appropriate arterial pressure since left atrial pressure was not determined and the amount of error introduced by failure to subtract such pressures is relatively small. In each animal, control determinations for cardiac output and coronary blood flow were made; then a peripheral vein in the foreleg was exposed and THAM † was given in a dose of 500 mg./kg. administered at a uniform rate with a constant injection syringe over a 30 minute period. The drug was dissolved in a volume of water sufficient that approximately 2 ml. of solution were given per minute throughout the infusion. This hypertonic solution was used in lieu of the larger volume of fluid which would have been required had an isotonic solution been given. In all the animals but the first, a supplemental dose was administered at the rate of 10 mg./kg./minute for the ensuing 20–25 minutes during the second determination of cardiac output and the coronary blood flow. The *p*H was measured in the femoral arterial and the coronary sinus blood specimens utilizing the Cambridge model r *p*H meter. Control studies were compared with the experimental studies utilizing the *t*-test.

† Tris (hydroxymethyl) aminomethane with electrolytes (tromethamine, Talatrol, THAM) was supplied by the Abbott Laboratories, North Chicago, Illinois, and contains per vial 18 g. of tromethamine, 0.87 g. of NaCl and 0.18 g. of KCl.

Results

Administration of THAM was accompanied by a significant increase in femoral arterial *p*H from 7.26 in the control state to 7.42 during

the drug administration. Coronary sinus *p*H increased similarly. Simultaneously cardiac rate increased significantly as shown in table 1. Although there was no change in systemic arterial blood pressure, pulmonary arterial and right atrial blood pressures decreased significantly. The minute volume of respiration decreased slightly, but not significantly. Body oxygen consumption was unchanged whereas carbon dioxide elimination was significantly reduced with a consequent considerable decrease in the exchange ratio or respiratory quotient. Since considerable increases occurred in the mixed venous, arterial, and coronary sinus carbon dioxide content, the reduced carbon dioxide elimination was due at least partially to its retention in the blood stream. Arterial, mixed venous, and coronary sinus oxygen content decreased, but neither the systemic nor the coronary arterio-venous oxygen difference changed significantly. With the retention of carbon dioxide in the body there was a decrease in the systemic arterio-venous carbon dioxide difference. The blood hemoglobin content and the hematocrit decreased significantly, probably as the result of the hypertonicity of the THAM solution.

The cardiac output did not change; nor did left or right ventricular work or total peripheral resistance. Total pulmonary resistance decreased slightly, but significantly, while coronary blood flow increased slightly, but not significantly. Cardiac oxygen consumption increased while the index of cardiac efficiency, which relates left ventricular work to left ventricular oxygen consumption declined slightly, but significantly.

Discussion

There is no doubt that administration of tris (hydroxymethyl) aminomethane (THAM) in the dose given to these experimental animals produces a significant increase in blood *p*H. Accompanying these changes in blood *p*H there is a significant increase in the carbon dioxide content of the blood and a decrease in respiratory quotient apparently as a result of the buffering action of THAM. Furthermore, a decrease occurred in arterial hematocrit and hemoglobin content indicating that hemodilution must have taken place secondary to the hypertonicity of the THAM solution.

In spite of the changes which occurred in the blood neither the body oxygen consumption nor arterio-venous oxygen difference changed during the study. Therefore, there is no quesiton as to the validity of the Fick principle for measuring cardiac output, even though carbon dioxide elimination did change significantly. Coronary blood flow increased slightly and cardiac oxygen consumption significantly subsequent to administration of THAM, but this may well be related to the increase in cardiac rate[16] rather than to a specific effect of THAM or the change in *p*H.

It is possible that both the increase in coronary blood flow and in cardiac rate were due to the decrease in hemoglobin and hematocrit secondary to hemodilution, but the response is greater than would be expected for the amount of change in oxygen carrying capacity. No correlation appeared to exist between the arterial oxygen saturation and the change in heart rate.

It is of interest that such a considerable change in blood *p*H had no effect on cardiac output. A similar change in *p*H (7.26 to 7.62) induced by passive hyperventilation in intact dogs had no significant effect on cardiac output or coronary blood flow.[17] Similarly active hyperventilation in man which induced a rise in *p*H from 7.41 to 7.63, produced no significant increase in cardiac output but decreased coronary flow slightly.[17] It should be noted that in the case of hyperventilation, the blood carbon dioxide content decreased markedly as contrasted with the increase in blood carbon dioxide content produced by administration of THAM.

A similar change in *p*H (7.28 to 7.45), induced in intact anesthetized dogs by intravenous administration of $NaHCO_3$, produced a 70 per cent increase in cardiac output, a 71 per cent increase in left ventricular work and a 46 per cent decrease in total peripheral resistance, while the blood carbon dioxide content rose significantly.[18] It should be pointed out in this context that the measured carbon dioxide content of the blood when THAM is given does not reflect the P_{CO_2} by usual nomograms, since, as a buffer, THAM vitiates ordinary extrapolations from the carbon dioxide and *p*H data. Indeed, THAM has been shown to decrease P_{CO_2} under conditions of apneic

oxygenation even though the plasma carbon dioxide content rises considerably.[6] The data from the experiments, then, as well as those obtained during hyperventilation,[17] and $NaHCO_3$ administration[18] are consistent with the hypothesis that increased P_{CO_2} is a vasodilator, whereas bound CO_2 has relatively little effect. They lend little support, however, to the idea that blood *p*H itself is an important determinant of hemodynamic parameters in the intact anesthetized animal at least over the usual, clinically encountered, ranges studied ehere. Indeed, in the intact anesthetized dog, under the conditions of these experiments, a significant increase in *p*H had very little hemodynamic effect.

Summary

The systemic and coronary hemodynamic effects of intravenous administration of trometharnine (THAM) has been studied in intact anesthetized mongrel dogs.

When approximately 750 mg./kg. of THAM was administered during a period of about 50 minutes, blood *p*H was significantly elevated.

The hemoglobin and hematocrit decreased, suggesting hemodilution.

In spite of the increased blood *p*H, significant changes did not occur in cardiac output, cardiac work, total peripheral resistance, coronary vascular resistance or coronary blood flow.

Cardiac rate and myocardial oxygen consumption increased significantly whereas cardiac efficiency was reduced, but this may well be a nonspecific effect due to hypertonicity or other characteristics of the THAM solution administered.

This study was supported in part by grants from the National Institutes of Health of the U.S.P.H.S., the Wisconsin Heart Association and the Wisconsin Alumni Research Foundation.

References

1. Gaskell, W. H.: On the tonicity of the heart and blood vessels, J. Physiol. 3: 48, 1880–2.
2. Darby, T. D., Aldinger, E. E., Thrower, W. B., and Westbrook, S. H.: Effects of tris (hydroxymethyl) aminomethane (THAM) on ventricular contractile force changes accompanying lactic acid infusion or elevation of ventilation CO_2. Fed. Proc. 19: 103, 1960 (abstract).
3. Jerusalem, E., and Starling, E. H.: On the significance of carbon dioxide for the heart beat, J. Physiol. 40: 279, 1910.
4. McElroy, W. T., Gerdes, R. J., and Brown, E. J., Jr.: Effects of CO_2, bicarbonate, and *p*H on the performance of isolated perfused guinea pig hearts, Amer. J. Physiology 195: 412, 1958.
5. Price, H. L., and Helrich, M.: The effect of cyclopropane, diethyl ether, nitrous oxide, thiopental and hydrogen ion concentration on the myocardial function of the dog heart-lung preparation, J. Pharmacol. Exp. Ther. 115: 206, 1955.
6. Bendixen, H. H., Laver, M. B., and Flacke, W. E.: Influence of respiratory acidosis on circulatory effect of epinephrine in dogs, Circulat. Res. 13: 64, 1963.
7. Brinkman, G. L., Remp, D. G., Coates, E. O., Jr., and Priest, E. McC.: The treatment of respiratory acidosis with THAM, Amer. J. Med. Sci. 239: 341, 1960.
8. Miller, R. A., Brindle, G. A., and Gilbert, R. G. B.: Studies with an organic buffer (THAM) during apneic oxygenation in dogs, Brit. J. Anaesth. 32: 248, 1960.
9. Nahas, G. G., and Ligou, J. C.: Effects of acute arterial blood *p*H changes on catecholamine plasma levels, and circulatory adaptations, Surg. Forum 10: 111, 1959.
10. Pierce, E. C.: The correction of acidosis with tris (hydroxymethyl) aminomethane, Arch. Surg. 80: 693, 1960.
11. Nahas, G. G.: The pharmacology of tris (hydroxymethyl) aminomethane (THAM), Pharmacol. Rev. 14: 447, 1962.
12. Van Slyke, D. D., and Neill, J. M.: The determination of gases in blood and other solutions by vacuum extraction and manometric measurement, J. Biol. Chem. 61: 523, 1924.
13. Scholander, P. F.: Analyzer for accurate estimation of respiratory gases in one-half cubic centimeter samples, J. Biol. Chem. 167: 235, 1947.
14. Orcutt, F. S., and Waters, R. M.: A method for determination of cyclopropane, ethylene, and nitrous oxide in blood with the Van Slyke-Neill manometric apparatus, J. Biol. Chem. 117: 509, 1937.
15. Altman, P. L., Dittmer, D. S., and Grebe, R. M.: Handbook of Circulation, Philadelphia, W. B. Saunders Co., 1959.
16. Maxwell, G. M., Castillo, C., White, D. H., Jr., Crumpton, C. W., and Rowe, G. G.: Induced tachycardia: its effect upon the coronary hemodynamics, myocardial metabolism and cardiac efficiency of the intact dog, J. Clin. Invest. 37: 1413, 1958.
17. Rowe, G. G., Castillo, C. A., and Crumpton, C. W.: Effects of hyperventilation on systemic and coronary hemodynamics, Amer. Heart J. 63: 67, 1962.
18. Maxwell, G. M., Rowe, G. G., Afonso, S., Crumpton, C. W., and Castillo, C. A.: The effect of sodium bicarbonate upon the general and cardiac hemodynamics and metabolism of the intact dog, Clin. Res. 7: 387, 1959 (abstract).