Systemic and Coronary Hemodynamic Effects of Trimethaphan Camphorsulfonate (Arfonad) in the Dog

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The acute systemic and coronary hemodynamic effects of Arfonad were determined in 10 intact anesthetized mongrel dogs. A sustained 35 per cent reduction in systemic arterial mean blood pressure was the end point of drug administration. The hemodynamic effects were consistent with peripheral pooling of blood, reduced central venous pressure and decreased cardiac work and coronary blood flow. The coronary sinus oxygen content decreased and cardiac efficiency was reduced. The results were basically similar to those obtained with longer acting ganglion blocking drugs.

THERE has been considerable interest in the hemodynamic effects of various ganglionic blocking agents and these data have been reviewed recently.[1] Although several studies have been done of the effects of trimethaphan camphorsulfonate (d-3,4(1′,3″ dibenzyl-2′-keto-imidazolido)-1,2 trimethylene thiophanium d-camphorsulfonate (Arfonad) on blood pressure,[2] cardiac output, [3,4] cerebral,[5,6,7] and renal blood flow,[3,4,7,8] its effects on the coronary circulation seem not to have been investigated. Consequently the present study was done.

Material and Methods

Ten mongrel dogs varying in weight between 17 and 30 kg. (average 23.8 kg.) were given 3 mg./kg. body weight of morphine sulfate subcutaneously followed one hour later by 0.25 ml./kg. intravenously of a 50/50 mixture of Dial-urethane and veterinary pentobarbital.* In the hour subsequent to achieving anesthesia, cardiac catheters were maneuvered fluoroscopically into the pulmonary artery, the coronary sinus, and the right atrium, and Cournand needles were inserted percutaneously into each femoral artery. One of the Cournand needles was attached to a manifold for aspirating blood specimens at intervals, and the other to a Statham strain gauge for monitoring of pressure. A peripheral vein was exposed in the foreleg and cannulated for administration of Arfonad. Cardiac output was then determined by the direct Fick principle, whereas coronary blood flow was determined by the nitrous oxide saturation method utilizing a partition coefficient of 1. All pressures were measured by means of Statham strain gauge pressure transducers recording on a Gilson macropolygraph. The mean pressures were determined by electrical damping of the pressure curve. Analyses of blood for carbon dioxide and oxygen were done by the Van Slyke-Neill method[9] and the nitrous oxide analyses were done by the method of Orcutt and Waters.[10] The oxygen and carbon dioxide content of expired air was determined by the Scholander method.[11] Whole blood *p*H was determined by the Cambridge model R *p*H meter. The formulas used for calculation are those generally used in hemodynamic studies.[12] Cardiac work was calculated by the Starling formula as the product of mean arterial blood pressure and cardiac output, utilizing appropriate constants to be expressed in kilogram meters of work per minute. Neither right nor left atrial blood pressure was substracted from the arterial blood pres-

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* Dial-urethane (Ciba Pharm. Products, Inc., Summit, N. J.) contains 100 mg. of Dial, 400 mg. of monoethylurea, and 400 mg. of urethane per milliliter. Veterinary pentobarbital contains 60 mg. of pentobarbital per milliliter.

sure in this calculation and changes in velocity were not computed. As is well known, neither of these constitute major errors in the present type of experiments.

After control observations on cardiac output and coronary blood flow had been made, an 0.5 or 1.0 per cent concentration of Arfonad in saline solution was administered to the animals by intravenous infusion. The rate of infusion was adjusted so as to reduce the mean blood pressure by approximately 35 per cent as determined by continuous inspection of the directly recorded systemic arterial pressure. There was considerable variability in the tolerance of various animals to Arfonad and a distinct tendency was noted for the animals to require progressively more rapid administration of the drug to maintain the same blood pressure reduction as the study progressed. Consequently, it is not possible to state the actual dose administered to each animal since the rate of administration varied in order to achieve a particular decrease in blood pressure. Since the end point of the administration was satisfactory control of blood pressure, as it is in usual clinical use, it is thought that the data acquired from these studies should be applicable during the customary use of Arfonad. The experimental observations on cardiac output and coronary blood flow were made after the blood pressure had been stable at its reduced level for approximately 5–10 minutes and extended over a period of 15–20 minutes.

Results

Results are summarized in table 1. As soon as the blood pressure began to decline with the administration of Arfonad, the pulse rate increased and at the time of the second study it was almost 50 per cent greater than during the control observations. If the rate of Arfonad administration were too rapid at the onset, blood pressure could be reduced to very low levels; however, this was avoided as carefully as possible and the level of mean arterial pressure was deliberately set at what was thought to be a reasonable level. In the completed series it was 34.2 per cent below the control ($P < 0.001$). The mean pulmonary arterial blood pressure was consistently reduced as well (−26.7 per cent, $P < 0.001$) and the right atrial pressure was markedly decreased (−57.1 per cent, $P < 0.01$). During the hypotensive phase, the respiratory rate and volume increased 54.5 per cent ($P < 0.001$) and 79 per cent ($P < 0.01$) respectively. Total body oxygen consumption and carbon dioxide excretion increased slightly but not significantly, and the respiratory quotient was unchanged. The arterial oxygen content increased slightly (+9.3 per cent, $P < 0.02$) and whereas there were trends for the hemoglobin (+7.1 per cent) and hematocrit (+9.8 per cent) to increase, neither of these changes were significant. The systemic arterio-venous oxygen difference increased (+39.5 per cent, $P < 0.01$) as did the arterio-venous oxygen difference across the myocardium (+26.1 per cent, $P < 0.01$). This increase in arterio-venous oxygen difference across the heart was due partly to the rise in arterial oxygen content and partly to the 28 per cent decrease in coronary sinus oxygen content ($P < 0.01$). Apparently associated with the hyperventilation, the mixed venous, systemic arterial and coronary sinus carbon dioxide content decreased significantly. Simultaneously the venous-arterial differences for carbon dioxide across the systemic and coronary circulation increased significantly. The cardiac respiratory quotient did not change significantly. Both femoral arterial and coronary sinus *p*H increased.

Calculations revealed that the cardiac output decreased by 24.2 per cent. Although reduction occurred in 8 of 10 animals, there was sufficient variation in this decrease that statistical significance was not reached ($P < 0.1$). Left ventricular work decreased 49 per cent ($P < 0.01$) whereas right ventricular work decreased 42.9 per cent ($P < 0.05$). Although total peripheral and total pulmonary resistance decreased somewhat, neither of these reductions were statistically significant. Coronary blood flow decreased 31.6 per cent ($P < 0.01$) which is approximately the same percentagewise as the reduction in cardiac output; however, the decrease in coronary flow was statistically significant because of its greater consistency. Coronary vascular resistance was essentially unchanged (−3.2 per cent). The left ventricular oxygen usage decreased 13.2 per cent,

TABLE 1. Systemic and Coronary Hemodynamic Effects of Arfonad
(Average figures for 10 dogs)

Parameter	Control ±S.D.*	Study ±S.D.*	S.E.M.† Difference	*P* Value <
Heart Rate (beats/minute)	91±20	136±26	7.689	0.001
Mean Arterial Blood Pressure (mm. Hg)	114±19	75±14	3.951	0.001
Mean Pulmonary Arterial Blood Pressure (mm. Hg)	15±2	11±2	0.789	0.001
Mean Right Atrial Blood Pressure (mm. Hg)	4.2±0.9	1.8±1.5	1.738	0.01
Minute Volume Respiration (liters/minute)	2.4±0.8	4.3±1.8	0.504	0.01
Respiratory Rate	11±5	17±4	1.195	0.001
Body Oxygen Consumption (ml./minute)	120±22	127±29	5.951	0.3
Body Respiratory Quotient	0.87±0.12	0.91±0.09	0.037	0.4
Arterial Oxygen Content (ml./100 ml. of blood)	17.2±1.9	18.8±2.5	0.553	0.02
Arterio-venous O_2 Difference (ml./100 ml. of blood)	3.8±0.7	5.2±1.1	0.334	0.01
Mixed Venous CO_2 Content (ml./100 ml. of blood)	50.5±4.7	45.4±5.1	1.033	0.001
Venous-Arterial CO_2 Diff. (ml./100 ml. of blood)	2.7±0.6	4.1±0.7	0.193	0.001
Coronary Sinus Oxygen Content (ml./100 ml. of blood)	5.7±1.4	4.1±0.6	0.438	0.01
Arterial-Coronary Sinus O_2 Diff. (ml./100 ml. of blood)	11.5±2.2	14.5±2.8	0.888	0.01
Coronary Sinus CO_2 Content (ml./100 ml. of blood)	57.2±5.1	53.7±5.6	0.830	0.01
Cardiac Respiratory Quotient	0.80±0.10	0.83±0.09	0.024	0.2
Arterial Hemoglobin (g./100 ml.)	14.1±1.7	15.1±2.3	0.484	0.1
Arterial Hematocrit (%)	41±5	45±7	1.461	0.1
Femoral Artery *p*H (units)	7.26±.05	7.28±.05	0.011	0.05
Cardiac Output (liters/minute)	3.3±1.2	2.5±0.8	0.357	0.1
Left Ventricular Work (kg. m./minute)	5.3±2.7	2.7±1.3	0.742	0.01
Right Ventricular Work (kg. m./minute)	0.7±0.4	0.4±0.2	0.127	0.05
Total Peripheral Resistance (c.g.s. units)	2941±754	2490±618	211.789	0.1
Total Pulmonary Resistance (c.g.s. units)	400±109	364±68	32.586	0.3
Coronary Blood Flow (ml./100 g./minute)	95±28	65±20	6.866	0.01
Coronary Vascular Resistance (units)	1.25±0.22	1.21±0.24	0.092	0.7
Left Ventricular Oxygen Usage (ml./100 g./minute)	10.6±2.4	9.2±3.1	0.658	0.1
Index of Efficiency (LVW÷LV O_2 Usage)	0.41±0.13	0.28±0.06	0.037	0.02

* S.D. = Standard Deviation.
† S.E.M. = Standard Error of the Mean.

but again variability precluded statistical significance. The calculated index of cardiac efficiency, however, which relates measured left ventricular oxygen consumption to left ventricular work, was significantly reduced (−31.7 per cent, $P < 0.02$).

Discussion

This study was done under morphine-Dial-urethane anesthesia because in dogs it produces a relatively stable state of anesthesia for a sufficient time to obtain meaningful results. The dogs usually have sinus arrhythmia with a well-controlled heart rate and their cardiovascular system remains responsive to many drugs. During the study ventilation usually increases slightly and especially does it increase if arterial pressure is significantly reduced. The changes in carbon dioxide which result from increased ventilation produce no significant change in control studies and appear to be an integral part of the overall response to hypotension. Such hypocapnia of itself does not seem to be hemodynamically significant.[13] Although in our experience dogs under the conditions of these experiments have shown the same type of hemodynamic response to ganglion blocking agents as that found in man, caution must always be observed when transferring interpretations of drug response from one species to another and from one experimental situation to another.

The present data concerning the regional blood flow through the coronary circulation are compatible with previous studies of cerebral blood flow subsequent to Arfonad administration. Thus it has been shown that early after the drug is given the cerebral blood flow decreases[5] or that the cerebral arterio-venous oxygen difference widens presumably because cerebral blood flow decreases[6, 7] whereas after

the hypotensive state has persisted for 30–60 minutes the cerebral vascular resistance decreases sufficiently that cerebral blood flow returns to, or toward, normal.[6, 7] Similarly renal blood flow decreases shortly after Arfonad administration and later returns toward normal.[8] The present study of coronary flow did not extend into the later readjustment period described in these previous studies but was confined to the earlier and apparently more critical primary adjustment phase. During the phase studied, coronary flow was significantly decreased.

The results of administration of Arfonad are similar in many respects to those which have been reported for longer acting ganglion blocking agents.[1, 14, 15] In general, in subjects without cardiac decompensation or mitral stenosis such agents produce a reduction in cardiac output and cardiac work.[1] Apparently the decreased output is related to several factors, probably chiefly the decrease in central venous pressure due to pooling of blood.[1, 16] Although at least hexamethonium has been shown to increase the force of contraction of the isolated heart preparation,[17] this does not exclude the possibility that *in vivo* the myocardial contractility is reduced secondary to decreased outflow through the sympathetic nervous system, with a resulting decreased catecholamine effect on the myocardium. Thus blocking of the sympathetic nerve endings decreases cardiac output and coronary blood flow as do ganglion blocking drugs.[18]

Total peripheral resistance decreased slightly but not significantly in the present study whereas in a preceding similar study with hexamethonium[14] a statistically significant increase in resistance occurred. Although experiments in open-chest dogs where the venous return could be controlled indicated that peripheral vascular resistance decreased subsequent to administration of several ganglion blocking drugs,[19] the cardiac output of these animals was so low and the control vascular resistance so high that it is difficult to apply the data to more physiologic situations. Arfonad has been reported previously to produce vasodilatation in the isolated denervated dog hind limb whereas tetraethylammonium chloride caused vasoconstriction.[2] This and other differences in these agents have been discussed previously[2] and offer a reasonable explanation for the relatively minor differences in the action of Arfonad and other ganglion blocking agents.

In spite of the considerable reduction in cardiac work, myocardial oxygen consumption did not decrease as much percentagewise, and in the face of decreased coronary blood flow, the coronary sinus oxygen content was significantly reduced. Undoubtedly part of the failure of myocardial oxygen consumption to follow the calculated external cardiac work is explained by the increase in cardiac rate, since cardiac oxygen consumption is closely related to cardiac rate.[20] It is reported that other ganglion blocking agents may be used for treatment of hypertension in subjects who have angina pectoris as well and that both conditions may be relieved.[21] Presumably this is possible because cardiac work is reduced into a range which is commensurate with attainable coronary blood flow. It is recommended by the manufacturer that Arfonad should not be used in subjects who have severe atherosclerosis or severe cardiac disease. These categories include most subjects with angina pectoris. It would seem that in the presence of rigid coronary arteries, coronary blood flow must depend chiefly on perfusion pressure and that until further information is available, the present demonstration in normal animals of reduced coronary blood flow, decreased coronary sinus oxygen content, maintained myocardial oxygen consumption and decreased cardiac efficiency support this warning. It should be emphasized, on the other hand, that repeated studies have shown no correlation between myocardial blood flow per unit weight and the presence of angina pectoris,[22] hence the present studies cannot be used as incontrovertible evidence that Arfonad is contraindicated in those with the anginal syndrome. Obviously further information concerning the mechanism of anginal pain is needed, but meanwhile the present data may be helpful in the use of Arfonad.

Conclusions and Summary

The acute systemic and coronary hemodynamic effects of trimethaphan camphorsulfonate (Arfonad) have been determined in 10 intact anesthetized mongrel dogs. The end point of drug administration was a sustained

35 per cent reduction in systemic arterial mean blood pressure. The hemodynamic effects were consistent with peripheral pooling of blood, reducing the central venous pressure and decreasing cardiac work and coronary blood flow. The coronary sinus oxygen content decreased and cardiac efficiency was reduced. The results are basically similar to those obtained with longer acting ganglion blocking drugs.

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References

1. Aviado, D. M.: Hemodynamic effects of ganglion blocking drugs, Circulat. Res. **8**: 304, 1960.
2. McCubbin, J. W., and Page, I. H.: Nature of the hypotensive action of a thiophanium derivative (RO 2-2222), J. Pharm. Exp. Ther. **105**: 437, 1952.
3. Eichna, L. W., Sobol, B. J., and Kessler, R. H.: Hemodynamic and renal effects produced in congestive heart failure by the intravenous administration of a ganglionic blocking agent, Trans. Ass. Amer. Physicians **64**: 207, 1956.
4. Sobol, B. J., Kessler, R. H., Rader, B., and Eichna, L. W.: Cardiac, hemodynamic and renal functions in congestive heart failure during induced peripheral vasodilatation; relationship to Starling's law of the heart in man, J. Clin. Invest. **38**: 557, 1959.
5. Moyer, J. H., and Morris, G.: Cerebral hemodynamics during controlled hypotension induced by the continuous infusion of ganglionic blocking agents (hexamethonium, Pendiomide and Arfonad), J. Clin. Invest. **33**: 1081, 1954.
6. Fazekas, J. F., Albert, S. N., and Alman, R. W.: The cerebral physiology of controlled hypotension, Arch. Surg. **73**: 59, 1956.
7. Parish, A. E., Kleh, J., and Fazekas, J. F.: Renal and cerebral hemodynamics with hypotension, Amer. J. Med. Sci., **233**: 35, 1957.
8. Moyer, J. H., McConn, R., and Seibert, R. A.: Effect of blood pressure reduction with Arfonad on renal hemodynamics and the excretion of water and electrolytes in patients with hypertension, Amer. Heart J. **49**: 360, 1955.
9. 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.
10. Orcutt, F. S., and Waters, R. M.: A method for the determination of cyclopropane, ethylene, and nitrous oxide in blood with the Van Slyke-Neill manometric apparatus, J. Biol. Chem. **117**: 509, 1937.
11. Scholander, P. F.: Analyzer for accurate estimation of respiratory gases in one-half cubic centimeter samples, J. Biol. Chem. **167**: 235, 1947.
12. Dittmer, D. S., and Grebe, R. S.: Handbook of Circulation. Philadelphia, W. B. Saunders Company, 1959, p. 355.
13. Rowe, G. G., Castillo, C. A., and Crumpton, C. W.: Effects of hyperventilation on systemic and coronary hemodynamics, Amer. Heart J., **63**: 67, 1962.
14. Crumpton, C. W., Rowe, G. G., O'Brien, G. S., and Murphy, Q. R., Jr.: The effect of hexamethonium bromide upon coronary flow, cardiac work, and cardiac efficiency in normotensive and renal hypertensive dogs, Circulat. Res., **2**: 79, 1954.
15. Rowe, G. G., Castillo, C. A., Maxwell, G. M., White, D. H., Jr., Freeman, D. J., and Crumpton, C. W.: The effects of mecamylamine on coronary flow, cardiac work and cardiac efficiency in normotensive dogs, J. Lab. Clin. Med. **52**: 883, 1958.
16. Rowe, G. G., Maxwell, G. M., Castillo, C. A., Freeman, D. J., and Crumpton, C. W.: Investigation of the mechanism of the hemodynamic effects of ganglionic blockade produced by mecamylamine, Amer. Heart J. **60**: 777, 1960.
17. Lee, W. C., and Shideman, F. E.: Inotropic action of hexamethonium, Circulat. Res. **6**: 66, 1958.
18. Rowe, G. G., Maxwell, G. M., Castillo, C. A., Clifford, J. E., and Crumpton, C. W.: Hemodynamic effects of β methyl-2, 6-dimethylphenylether of choline (SKF 6890) on the systemic and coronary circulations, J. Lab. Clin. Med. **56**: 409, 1960.
19. Trapold, J. H.: Role of venous return in the cardiovascular response following injection of ganglion-blocking agents, Circulat. Res. **5**: 444, 1957.
20. Maxwell, G. M., Castillo, C. A., 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.
21. Doyle, A. E., and Kilpatrick, J. A.: Methonium compounds in the angina of hypertension, Lancet **1**: 905, 1954.
22. Rowe, G. G.: The regulation of coronary blood flow in man in normal and abnormal conditions, Med. Clin. N. Amer. **46**: 1421, 1962.