Systemic and Coronary Hemodynamic Effects of Hexadylamine. * (28100)

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It has long been considered that an ideal coronary vasodilator should produce an increase in coronary blood flow and coronary sinus blood oxygen content without producing an increase in cardiac oxygen consumption. Thus the over-all myocardial oxygen tension should be increased without a concomitant increase in cardiac work. This type of response has been referred to as "benign" coronary vasodilation and differs from "malignant" coronary vasodilatation in which, characteristically, coronary blood flow increases to meet greater myocardial oxygen consumption and the coronary sinus blood oxygen content is reduced(1). These concepts reveal the necessity for consideration of the hemodynamic effects of coronary dilators in their entirety rather than by scattered observations in isolated circulatory beds. When hexadylamine (MRL 38, dicyclohexylpiperidyl-ethylene hydrochloride) became available for investigation as a coronary vasodilator, the present study was undertaken to evaluate its systemic and coronary hemodynamic effects in the intact animal.

Material and methods. Ten mongrel dogs weighing between 18 and 26 kg (average 21.3 kg) were given 3 mg/kg body weight of morphine subcutaneously, followed one hour later by 0.25 mg/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, coronary sinus and right atrium and Cournand needles were inserted percutaneously into each femoral artery. Cardiac output was then determined by the Fick principle. Coronary blood flow was determined by the nitrous oxide saturation method utilizing a partition coefficient of one. Pressures were measured through the cardiac catheters and the femoral arterial needle by means of Statham strain gauge pressure transducers recording on a Gilson macropolygraph. The mean pressure was determined by electrical integration of the pressure curve. Analyses of blood for carbon dioxide and oxygen were done by the Van Slyke-Neill method, whereas nitrous oxide analyses were done by the method of Orcutt and Waters. Oxygen and carbon dioxide content of expired air was determined by the Scholander method. Whole blood pH was determined by the Cambridge Model R pH meter. The formulae used for calculations are those generally used. Cardiac work was calculated by the Starling formula as the product of mean arterial blood pressure and cardiac output with appropriate constants to be expressed in kilogram meters but without subtracting either right or left atrial pressure. Hexadylamine was dissolved in physiological saline solution and injected through a fourth cardiac catheter with its tip in the right atrium at a rate of 0.4 mg/kg/min beginning 5 minutes before the experimental study and continuing throughout the second determination of cardiac output and coronary flow.

Results. The results are summarized in Table I. Administration of hexadylamine produced an increase in cardiac rate and cardiac output, accompanied by a decrease in total peripheral resistance and mean systemic arterial blood pressure. Pulmonary arterial pressure rose slightly but insignificantly whereas total pulmonary resistance was significantly reduced. Mean right atrial pres-

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† Dial-urethane, furnished by the courtesy of Dr. A. J. Plummer, CIBA Pharmaceutical Products, Inc., Summit, N. J., contains Dial (di-allyl barbituric acid) 100 mg/ml, monethylurea 400 mg/ml, and urethan 400 mg/ml. Veterinary pentobarbital contains 60 mg/ml of pentobarbital.

TABLE I. Systemic and Coronary Hemodynamic Effects of Hexadylamine on the Dog.

Parameter	Control ± SD*	Exp ± SD*	SEM diff†	% change	P value <
Heart rate (beats/min)	70 ± 15	97 ± 16	5.136	+38.6	.001
Mean systemic arterial blood pressure (mm Hg)	129 ± 20	118 ± 17	2.357	- 8.5	.01
Mean pulmonary arterial blood pressure (mm Hg)	15 ± 4	19 ± 8	1.528	+26.7	.1
Mean right atrial blood pressure (mm Hg)	3.6 ± 1.4	3.3 ± 1.5	.254	- 8.3	.3
Oxygen consumption (ml/min)	101 ± 15	111 ± 15	2.413	+ 9.9	.01
Respiratory quotient	.79 ± .02	.85 ± .09	.014	+ 7.6	.01
Arterial oxygen content (ml/100 ml of blood)	18.6 ± 1.4	19.1 ± 1.0	.288	+ 2.7	.2
Arterial CO_2 content (ml/100 ml of blood)	49.6 ± 3.3	47.6 ± 4.0	.523	- 4.0	.01
Coronary sinus O_2 content (ml/100 ml of blood)	6.4 ± 2.3	10.6 ± 3.2	1.143	+65.6	.01
Arterial hematocrit (%)	46 ± 4	47 ± 2	.789	+ 2.2	.05
Cardiac output (l/min)	2.3 ± .5	3.0 ± 1.1	.249	+30.4	.02
Left ventricular work (kg M/min)	4.0 ± 1.2	4.9 ± 2.2	.448	+22.5	.2
Right ventricular work (kg M/min)	.5 ± .2	.8 ± .7	.144	+60.0	.05
Total peripheral resistance (cgs units)	4622 ±947	3464 ±1109	217.152	- 25.1	.001
Total pulmonary resistance (cgs units)	544 ±130	509 ± 151	14.773	- 6.4	.05
Coronary blood flow (ml/100 g/min)	78 ± 23	118 ± 34	11.971	+51.3	.01
Left ventricular O_2 usage (ml/100 g/min)	8.8 ± 1.8	10.0 ± 3.1	1.034	+13.6	.3
Cardiac respiratory quotient	.78 ± .05	.84 ± .09	.024	+ 7.7	.05
Coronary vascular resistance (units)	1.74 ± .5	1.06 ± .2	.173	- 39.1	.01
Index of efficiency (LVW ÷ LV O_2 usage)	.46 ± .07	.49 ± .14	.041	+ 6.5	.4

* SD = Standard deviation. † SEM = Standard error of mean.

sure decreased. The minute volume of respiration increased, accompanied by an increase in consumption of oxygen and excretion of carbon dioxide. The body respiratory quotient rose while the systemic arterial, and mixed venous carbon dioxide contents decreased. Left ventricular work was increased slightly but not significantly whereas right ventricular work increased more percentagewise and reached statistical significance. No significant change occurred in femoral arterial or coronary sinus pH. There was a small, but consistent increase in arterial hematocrit.

Coronary blood flow increased significantly accompanied by an increase in coronary sinus oxygen content and decrease in the myocardial arterio-venous oxygen difference and coronary vascular resistance. The cardiac respiratory quotient rose similarly to the body respiratory quotient. The index of efficiency, which relates myocardial oxygen consumption to left ventricular work, was unchanged. It should also be indicated that coronary flow per unit of oxygen consumed by the left ventricle increased significantly (+40%, $p < 0.05$) whereas coronary flow per unit of left ventricular work did not increase significantly (+38%, $p < 0.1$) and coronary flow per cardiac cycle was essentially unchanged (+7.0%, $p < 0.7$).

Discussion. In the intact anesthetized dog under the conditions of these experiments, hexadylamine produced significant systemic and coronary vasodilatation. Furthermore, after hexadylamine, the myocardial oxygen supply exceeded the demand so that the cor-

onary sinus blood oxygen content rose. This hemodynamic pattern is significantly different from that which has been reported in man for nitroglycerin(2,3) and erythrol tetranitrate(4), since neither of these agents produced an increase in coronary sinus blood oxygen content. Furthermore, after nitrates, left ventricular work and cardiac output are decreased(2,3,4) whereas after hexadylamine cardiac output increased significantly and left ventricular work tended to increase. Although nitroglycerin is reported to increase coronary flow of normal human subjects(2), no such change was observed in those with angina pectoris(3) in spite of the fact that their coronary blood flow can be increased as shown by the response during exercise(5). Erythrol tetranitrate did not increase coronary flow in either normal subjects or those with angina pectoris. In the present experiments, then, hexadylamine would appear to be significantly different from nitroglycerin and erythrol tetranitrate.

Whether hexadylamine will be effective in relieving anginal pain must be determined clinically, since at present there is no clear cut relationship between coronary blood flow and angina pectoris(5,6,7) and since hydralazine, which increases coronary blood flow and coronary sinus blood oxygen content(8) is prone to precipitate anginal pain in susceptible subjects.

Summary. 1. Systemic and coronary hemodynamics have been determined in a series of 10 intact anesthetized mongrel dogs by the Fick principle and nitrous oxide method respectively, before and during a constant intravenous infusion of hexadylamine (MRL 38, dicyclohexyl-piperidyl-ethylene hydrochloride). 2. Administration of hexadylamine produced peripheral and coronary vasodilatation, as well as increased cardiac output and coronary blood flow. 3. The coronary sinus oxygen content increased significantly, with narrowing of the myocardial arteriovenous oxygen difference. 4. Left ventricular work and myocardial oxygen consumption increased slightly but insignificantly.

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Amount of Residual Blood in Rabbit Organs After Acute Lethal Hemorrhage. (28101)

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Many studies with labelled proteins in recent years have been concerned with their partition between blood and extravascular space in man and in animals, this being determined by difference from measurements made in the plasma before and after equilibrium is established. It is highly desirable to extend these studies to individual organs so that a detailed picture of lymphatic distribution of proteins can be pieced together. Since it is seldom practical to wash out the blood trapped in organs we have preferred to introduce a second isotopic indicator injected just before death to measure its amount. During