SYSTEMIC AND CORONARY HEMODYNAMIC EFFECTS OF ERYTHROL TETRANITRATE *

By GEORGE G. ROWE, CARL J. CHELIUS, SKODA AFONSO, HANS P. GURTNER AND CHARLES W. CRUMPTON

(From the Cardiopulmonary Research Laboratory and the Department of Medicine of the University of Wisconsin, Madison, Wis.)

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Data in experimental animals have indicated that an increase in coronary blood flow occurs subsequent to the administration of nitrates into the coronary vessels (1), but injection of substances into the coronary vessels may have quite a different effect than have systemic administrations of the same agents in either animals or man. Hemodynamic studies of the adjustment to sublingual nitroglycerin administration in man have shown decreased cardiac output (2) and left ventricular work (2, 3). Coronary blood flow increased in normal subjects (3), but not in subjects with angina pectoris (2). It has been deduced from these observations that the mechanism of nitrites in relieving angina pectoris may be through reduction in cardiac work rather than any specific effect on the coronary circulation itself (2). The literature has been ably reviewed recently (2, 3) and will not be reviewed again here.

Since the period of action of nitroglycerin is transient (4) and since the nitrous oxide method requires a rather prolonged plateau of effect in order to permit its accurate use, a longer-acting agent, erythrol tetranitrate, was studied.

MATERIAL AND METHODS

The present investigation was done on 15 subjects; 5 of these were normal individuals as far as the cardiovascular system was concerned. Four subjects (group A) had arterial hypertension, but since they did not have angina pectoris they are hereinafter called "controls." Four subjects were hospitalized because of angina pectoris; Subject 1316 had previously been hospitalized for "pericardial poudrage" and Subject 1299 had had I^{131} therapy as a therapeutic measure for angina pectoris, but the other two had had no treatment other than the usual medical treatment for this disease. All subjects were studied in the fasting state without premedication, and a concerted effort was made by reassurance to achieve a basal state.

In order to facilitate the procedure, two cardiac catheters were used in most subjects. These were introduced through the same vein, or two adjacent veins in the same small surgical field, and manipulated so that the first catheter lay in the pulmonary artery and the second in the coronary sinus. A needle tip was placed percutaneously in the femoral artery. Cardiac output was done by the Fick principle in all cases except one in which, due to an anomaly of the course of the superior vena cava, the catheter could not be manipulated into the pulmonary artery. In this subject (1299) cardiac output was done by the Hamilton indicator dilution method utilizing the Gilford densitometer and indocyanine green. In one of the control subjects who developed venous spasm (1312), catheterization of the coronary sinus was unsuccessful, so the second catheter was withdrawn and cardiac output alone was determined. In Subject 1274 with angina pectoris, the data on cardiac output are incomplete. Coronary blood flow was determined by the nitrous oxide saturation method with a partition coefficient of 1. Pressures were recorded through Statham strain gages on a Waters photographic recorder. Expired air was collected in a Tissot spirometer and analyzed for oxygen and carbon dioxide by the method of Scholander. Blood gas analyses were done by the Van Slyke-Neill method and nitrous oxide analyses were done by the method of Orcutt and Waters (5). All blood gas analyses for oxygen and carbon dioxide are done in duplicate, and oxygen determinations are required to check within 0.2 vol.

In 9 subjects, subsequent to the administration of 7.5 to 15 mg erythrol tetranitrate under the tongue, blood pressure, pulse and respiration were observed and revealed no major untoward changes; these subjects are grouped together for purposes of statistical analysis. In 3 subjects, 1 of whom had no known cardiovascular disease and 2 with known angina pectoris, a marked hypotensive reaction occurred, accompanied by a slow heart rate, marked systemic symptoms of discomfort and a "shock-like" state; these subjects are considered separately from the rest, since it is believed that their reaction was sufficiently different clinically from the other group that it would be unwise to include all the data in the same calculations.

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TABLE I

Systemic and coronary hemodynamic effects of erythrol tetranitrate

Group, Cath. no. Subject data		Sex	Age	BSA	Dose	Time drug to study	Mean blood pressure			Heart rate	Min vol. resp	$\dot{Q}_{O_2}$	R.Q.	Art. O_2 content	Arterio-ven. O_2 diff.	Mixed ven. CO_2 content	Mixed venous art. CO_2 diff.	Cor. sinus O_2 content	Cor. sinus CO_2 content
							Art.	Pulm.	Cor. sinus										
Group A			*yrs*	m^2	*mg*	*min*		*mm Hg*			*L/min*	m^2 *BSA*		*ml/100 ml of blood*					
1256 Normal	C	♂	41	2.09	15	16	122	17	7.0	79	3.9	118	0.57	18.2	4.1	46.2	2.4	5.3	53.5
	D						111	12	3.5	92	6.4	162	0.74	18.4	4.1	45.9	2.9	6.0	52.0
1284 Normal	C	♂	45	1.75	15	8	88	15	2.8	70	6.4	165	0.73	21.0	4.4	44.4	3.1	5.8	52.3
	D						74	12	1.5	80	7.0	155	0.82	20.8	5.0	43.5	3.9	5.8	49.0
1292 Hyperten.	C	♀	47	1.59	15	13	157	24	8.5	82	6.5	134	0.91	16.2	4.2	53.5	3.5	4.0	59.3
	D						135	13	3.3	96	7.1	156	0.80	16.2	4.4	51.4	3.9	3.9	57.3
1295 Hyperten.	C	♀	40	2.08	15	14	135	14	1.3	101	5.3	133	0.74	18.6	3.5	49.9	2.5	4.7	56.4
	D						118	9	0.8	111	5.4	125	0.79	18.4	5.2	49.1	3.6	4.8	56.0
1315 Normal	C	♀	43	1.57	15	21	82	13	1.3	83	5.3	126	0.63	15.7	3.9	52.4	2.7	3.9	57.5
	D						77	8	1.0	127	6.6	132	0.74	14.6	4.3	53.8	2.9	4.1	58.6
1328 Hyperten.	C	♀	31	1.64	7.5	21	153	19	7.0	81	6.0	137	0.77	17.2	3.3	47.3	3.0	4.6	53.7
	D						141	14	3.5	84	6.0	144	0.76	16.9	4.5	46.7	2.9	4.5	52.7
1320 Hyperten.	C	♀	68	1.70	7.5	16	132	14	2.1	90	4.6	140	0.70	15.5	3.5	53.4	2.2	5.1	59.6
	D						92	8	1.2	100	4.5	130	0.65	15.0	5.8	53.3	4.0	4.1	57.8
1324 Normal	C	♂	26	1.90	7.5	7	86	14	4.2	77	5.2	166	0.70	22.3	3.1	52.1	2.3	11.1	56.7
	D						81	11	1.0	83	5.2	165	0.63	22.3	4.6	49.4	2.6	11.8	55.1
1300 Normal	C	♀	80	1.83	7.5	13	123	17	7.5	72	6.9	144	0.85	16.4	4.3	54.2	3.2	3.7	59.4
	D						106	11	3.7	81	5.4	131	0.70	15.8	4.7	54.2	2.6	4.3	59.3
Average control (before)							120	16	4.6	82	5.6	140	0.73	17.9	3.8	50.4	2.8	5.4	56.5
Average study (after)							104	11	2.2	95	6.0	144	0.74	17.6	4.7	49.7	3.3	5.5	55.3
% Change							−13.3	−31.3	−52.2	+15.9	+7.1	+2.9	+1.4	−1.7	+23.7	−1.4	+17.9	+1.9	−2.1
p <							0.01	0.001	0.01	0.02	0.4	0.6		0.1	0.01	0.2	0.1	0.6	0.05
Group B, "Shock"																			
1335 Normal	C	♀	61	1.73	7.5	35	85	11	1.5	68	3.9	112	0.78	15.4	3.8	51.5	1.9	4.8	57.3
	D						63	8	0.8	61	3.4	98	0.70	14.7	4.8	50.4	2.7	4.8	56.0
1299 Angina	C	♂	52	1.85	15	17	106			60								5.6	59.0
	D						58			60								5.1	58.0
1316 Angina	C	♂	66	1.91	15	20	155	40	9.0	84	5.7	163	0.74	17.5	5.5	54.6	4.0	5.7	59.0
	D						70	10	1.0	67	4.3	140	0.53	16.5	6.1	49.2	2.8	5.3	50.1
Group C, No "shock"																			
1263 Angina	C	♂	44	1.83	15	19	107	17	5.5	72	8.3	145	0.77	18.3	4.0	42.2	3.0	5.8	49.4
	D						107	13	4.0	77	7.2	146	0.63	18.2	4.3	41.4	2.8	7.7	48.3
1274 Angina	C	♂	57	2.08	15	14	137	17	5.5	76	7.2	147	0.80	19.1	4.0	55.6	4.9	5.4	63.1
	D						126	14	5.5	90				19.4	5.7	53.9	5.3	4.9	61.3
Group D, Incomplete																			
1312 Normal	C	♀	38	1.80	15	28	139	17		72	5.6	139	0.76	15.5	3.6	51.9	3.2		
	D						153	12		93	4.4	108	0.74	15.6	4.6	49.5	3.0		

TABLE I—(*Continued*)

Group, Cath. no. Subject data		Sex	Age	Art. Hb	Art. hct	Art. pH	Cor. sinus pH	Card. index	LV work index	RV work index	Total periph. resist.	Total pulm. resist.	Cor. blood flow	LV $\dot{Q}_{O_2}$	Cardiac R.Q.	Cor. vasc. resist.	Index effic.
Group A			*yrs*						*kg-m/min*			cg	*ml/100g/min*				
1256	C	♂	41	14.4	45			2.9	4.8	0.7	1625	226	72	9.6	0.71	1.69	0.50
Normal	D			14.4	46			4.0	6.0	0.6	1072	116	85	10.7	0.77	1.31	0.56
1284	C	♂	45	17.3	53	7.47	7.38	3.7	4.5	0.8	1880	321	71	10.5	0.77	1.24	0.43
Normal	D			17.0	52	7.50	7.45	3.1	3.1	0.5	1910	310	73	10.7	0.76	1.01	0.29
1292	C	♀	47	12.9	41	7.36	7.32	3.2	6.8	1.1	2474	378	108	13.0	0.84	1.45	0.52
Hyperten.	D			13.0	41	7.39	7.36	3.5	6.5	0.6	1914	184	123	15.0	0.79	1.10	0.43
1295	C	♀	40	14.6	45	7.46	7.43	3.8	7.0	0.7	1363	141	112	15.7	0.74	1.21	0.45
Hyperten.	D			14.3	45	7.43	7.43	2.4	3.9	0.3	1879	143	109	14.5	0.74	1.08	0.27
1315	C	♀	43	11.5	37	7.53	7.44	3.2	3.6	0.6	1291	205	83	9.8	0.65	0.99	0.37
Normal	D			11.2	36	7.43	7.39	3.1	3.2	0.3	1278	133	103	11.2	0.67	0.75	0.29
1328	C	♀	31	13.8	44	7.39	7.39	4.2	8.7	1.1	1793	223	119	15.1	0.76	1.29	0.58
Hyperten.	D			13.7	44	7.41	7.37	3.2	6.1	0.6	2134	213	112	13.7	0.77	1.25	0.45
1320	C	♀	68	12.2	38	7.40	7.36	4.0	7.2	0.8	1551	164	122	13.1	0.82	1.08	0.55
Hyperten.	D			11.9	37	7.41	7.38	2.2	2.8	0.2	1930	167	80	8.6	0.78	1.15	0.42
1324	C	♂	26	17.6	58	7.40	7.37	5.3	6.3	1.0	676	110	68	7.8	0.73	1.26	0.81
Normal	D			17.6	58	7.41	7.39	3.6	3.9	0.5	948	129	76	9.7	0.65	1.07	0.40
1300	C	♀	80	12.8	40	7.50	7.43	3.4	5.6	0.8	1601	221	120	15.2	0.76	1.03	0.37
Normal	D			12.5	40	7.46	7.42	2.8	4.0	0.4	1659	172	133	15.0	0.69	0.80	0.27
Average control (before)				14.1	45	7.44	7.39	3.7	6.1	0.8	1584	221	97	12.2	0.75	1.25	0.51
Average study (after)				14.0	44	7.43	7.40	3.1	4.4	0.4	1636	174	99	12.1	0.74	1.06	0.38
% Change				−0.7	−2.2	−0.1	+0.1	−16.2	−27.9	−50.0	+3.3	−21.3	+2.1	−0.8	−1.3	−15.2	−25.5
$p <$				0.2	0.4	0.6	0.5	0.1	0.02	0.001	0.7	0.1	0.8	0.9	0.3	0.01	0.02
Group B, "Shock"																	
1335	C	♀	61	11.8	39	7.40	7.36	2.9	3.4	0.5	1338	173	64	6.8	0.73	1.33	0.50
Normal	D			11.8	38	7.35	7.31	2.0	1.7	0.2	1422	181	43	4.3	0.77	1.47	0.40
1299	C	♂	52	14.6	43	7.32	7.29	2.6	3.8		1749		73	9.2	0.79	1.45	0.41
Angina	D			14.3	43	7.35	7.31	1.6	1.2		1584		60	7.5	0.74	0.97	0.16
1316	C	♂	66	14.1	45	7.41	7.37	3.0	6.3	1.6	2184	564	146	17.4	0.87	1.06	0.36
Angina	D			13.3	42	7.54	7.54	2.3	2.2	0.3	1273	182	35	4.2	0.75	2.00	0.52
Group C, No "shock"																	
1263	C	♂	44	14.3	45	7.41	7.36	3.6	5.2	0.8	1296	206	97	11.8	0.89	1.10	0.44
Angina	D			14.4	46	7.41	7.35	3.4	4.9	0.6	1384	168	100	10.2	0.84	1.07	0.48
1274	C	♂	57	15.5	45	7.47	7.44	3.7	6.9	0.9	1431	146	59	8.5	0.69	2.32	0.81
Angina	D			15.3	45	7.47	7.44						64	9.4	0.75	1.97	
Group D, Incomplete																	
1312	C	♀	38					3.9	7.3	0.9	1593	195					
Normal	D							2.4	4.9	0.4	2885	226					

RESULTS

The results are summarized in Table I for the nine control subjects without adverse reaction; figures for those with angina pectoris, those with the "shock-like" state, and the one normal who had only determination of cardiac output are included at the bottom of the table for further discussion. Data as presented in the results will refer to the nine control subjects unless otherwise stated.

Cardiac rate increased by 15.9 per cent ($p < 0.02$), whereas the mean pressure decreased in the systemic arteries ($-$ 13.3 per cent, $p < 0.01$), pulmonary artery ($-$ 31.3 per cent, $p < 0.001$) and coronary sinus ($-$ 52.2 per cent, $p < 0.01$). Coronary sinus pressure ordinarily follows right atrial pressure so closely that it may be taken as a reflection of central venous pressure. The minute volume of respiration and the respiratory rate did not change and there were no significant differences in oxygen consumption, carbon dioxide excretion or respiratory quotient. The hemoglobin decreased very slightly, but consistently, so that the change was statistically significant. The hematocrit decreased similarly, but less consistently and was not significant. pH in the arterial and coronary sinus blood did not alter. The arterial oxygen content did not change significantly, but the mixed venous oxygen content decreased ($-$ 8.5 per cent, $p < 0.01$) and the arteriovenous oxygen difference increased ($+$ 23.7 per cent, $p < 0.01$). The arterial carbon dioxide content decreased ($-$ 2.5 per cent, $p < 0.05$), but the widening of the venous-arterial carbon dioxide difference was sufficiently variable that the increase ($+$ 17.9 per cent) was not statistically significant ($p < 0.1$). Coronary sinus oxygen content and arterial coronary sinus oxygen difference did not change significantly.

The cardiac index decreased insignificantly in nine controls ($-$ 16.2 per cent, $p < 0.1$), but the cardiac index of the total group of 14 observations decreased significantly ($-$ 20.3 per cent, $p < 0.01$). Because of the increase in cardiac rate, accompanied by the decrease in cardiac output, stroke index in the controls was significantly reduced ($-$ 26.1 per cent, $p < 0.01$). Neither the total peripheral resistance nor the total pulmonary resistance changed significantly. The left ventricular work index decreased ($-$ 27.9 per cent, $p < 0.02$) and the left ventricular stroke work index was reduced even further ($-$ 35.1 per cent, $p < 0.01$). Similarly, right ventricular work index decreased ($-$ 50.0 per cent, $p < 0.001$).

The coronary blood flow in the controls remained unchanged as did the left ventricular oxygen consumption, carbon dioxide liberation and respiratory quotient. Coronary vascular resistance, on the other hand, decreased significantly ($-$ 15.2 per cent, $p < 0.01$) and the index of efficiency, calculated as the amount of work done by the left ventricle per unit of oxygen consumed by each 100 g of left ventricle, decreased ($-$ 25.5 per cent, $p < 0.02$). Coronary blood flow divided by heart rate decreased slightly ($-$ 10.5 per cent) but not significantly ($p < 0.1$).

The coronary blood flow of the subjects who had marked hypotension decreased considerably ($-$ 50 per cent) but the small number (three) justify no statistical evaluation. In spite of the adverse effects on these subjects (pallor, diaphoresis, confusion, nausea, cutaneous paresthesias), anginal pain was not experienced. In this regard the marked reduction in left ventricular work should be noted ($-$ 62.5 per cent). Symptomatic improvement with increased blood pressure occurred very quickly on administration of 100 per cent oxygen by mask, and there were no sequellae. In the two subjects with angina pectoris in whom severe hypotension did not occur, coronary blood flow did not change significantly. In one of these subjects, through error, the final reading on the Tissot spirometer was not recorded, hence cardiac output can not be calculated. If one presumes, however, in this subject that oxygen consumption did not change, since it did not in the other subjects, cardiac output decreased in both subjects with angina and the hemodynamic effects of the drug are the same as in the "controls."

DISCUSSION

The usual effectiveness of nitrates in the treatment of angina pectoris remains unquestioned in the mind of the clinician and the subject with angina pectoris. However, the mechanism of their action may require re-evaluation, since the studies of nitroglycerin reported previously (2, 3) and

those currently reported for erythrol tetranitrate indicate that an increase in coronary blood flow is unlikely to be the explanation for this beneficial effect. It was concluded recently that nitroglycerin might be effective in treatment of angina pectoris because it reduced the cardiac work to a level which could be adequately supported by the unaltered coronary blood flow (2).

The mechanism of reduction of cardiac output seems to be related to the decrease in the central venous filling pressure, apparently due to pooling of blood within the venous system. Associated with this reduction in the central venous filling pressure, the cardiac stroke volume falls off markedly. Even though a compensatory increase occurs in cardiac rate, the cardiac output is not maintained, and in the over-all group reported here cardiac output and work decreased. It is noted that in those subjects who did not develop a compensatory tachycardia there was a marked, untoward fall in blood pressure with a "shock-like" state. Furthermore, in these "shocked" subjects withdrawal of relatively small volumes of blood was associated with a further decrease in arterial pressure.

It should be noted that, in the present study as in previous studies of nitrate administration in experimental animals (6, 7), myocardial oxygen consumption did not change. The previous report of an increase in myocardial oxygen consumption subsequent to nitroglycerin administration was found in "normal" (2) but not in abnormal human subjects (3). The reason for this discrepancy remains obscure.

It is of considerable interest that, although calculated peripheral resistance did not change, the resistance to coronary blood flow decreased in most of the subjects, including the two with angina pectoris, unless there was an excessive hypotensive response. Since coronary flow was maintained with a lower perfusion pressure, there must have been an increase in cross section area of the coronary vessels. This is compatible with previous measurement of coronary flow in intact animals (4), angiographic demonstration in animals of an increase in size of the coronary arteries subsequent to the administration of nitrates into the coronary arteries (8), and the direct demonstration *in vitro* of dilatation of rings of coronary arteries when nitrates are introduced into the suspending solution (9). The latter two of these reports (8, 9), however, are to some extent less significant in that the response of the coronary vessels was not determined in relation to the rest of the vessels of the body. It seems, therefore, from the present study that the integral parts of the mechanism of action of erythrol tetranitrate in angina pectoris are reduction in cardiac work and decreased coronary vascular resistance, permitting sufficient coronary blood flow to sustain the reduced cardiac work load.

CONCLUSIONS

1. The systemic and coronary hemodynamic effects of erythrol tetranitrate have been investigated in 15 subjects.

2. Cardiac output was reduced, as was blood pressure in the systemic and pulmonary arteries and the coronary sinus.

3. Coronary blood flow was unchanged but coronary vascular resistance was reduced.

4. Myocardial oxygen consumption was unchanged and cardiac efficiency was lowered.

5. The hypothesis that the effectiveness of nitrites is due to the reduction in cardiac work into a range commensurate with an attainable coronary blood flow is supported by these findings.

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