Hypothermia: I. Effect on Renal Hemodynamics and on Excretion of Water and Electrolytes in Dog and Man * †

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HYPOTHERMIA is frequently used during vascular surgery in an attempt to reduce the metabolic demands of isolated vascular beds which are subjected to ischemia when vascular occlusion is required. Since homograft replacement of the abdominal aorta, as well as the thoracic aorta, is now feasible, it frequently becomes necessary to interrupt the blood supply to the kidney. When the renal ischemia is prolonged, it may lead to renal failure; therefore any method for reducing the renal damage during this period of ischemia would be of advantage to the surgeon. Likewise, the effect of reduction of body temperature alone should be known. The following study was undertaken in an attempt to study the effects of reduction in body temperature on renal function both in laboratory animals[4] and in patients who subsequently had vascular operations.

METHODS AND MATERIALS

Laboratory Observations. Thirty-nine dogs varying in weight from 10 to 23 kilograms were subjected to hypothermia. The animals have been divided into four different groups, each group used for a different type of observation. Some of the animals appear in more than one group of observations. Observations were made on the blood pressure, glomerular filtration rate, renal blood flow, maximum tubular function (TmG) and excretion of water and electrolytes.

Group I consisted of nine animals (Tables 1A and 1B) in which the effect of progressive reduction of body temperature on renal function was observed. Following suitable control observations, the temperature was reduced progressively to 26.7° C. (80° F.). Observations during hypothermia were made at 90° F., 85° F., and 80° F. The observations consisted of mean blood pressure, glomerular filtration rate, renal blood flow and excretion of water and electrolytes.

Group II consisted of 31 animals (Tables 2A and 2B) in which the effect of reduction of body temperature to 26.7° C. was observed (Sub-group 2A, 2B and 2C). In ten of these animals (Group 2C) the response to hypothermia alone was observed. In another ten animals (Sub-group 2A) the effect of prolonged hypothermia for one hour or more was observed (Period D4, Dogs No. 10–19). Following the observations at hypothermic levels for one hour or more, the temperature was then increased to normothermic levels in these animals. In the 11 dogs in Sub-group 2B, the temperature was also reduced to 26.7° C. but was returned to control levels immediately after the observations at hypothermic levels were completed. The observations made during varying periods of hypothermia were then compared with the control values as well as the values obtained following the re-

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TABLE 1A. *Effect of Progressive Reduction of Body Temperature on Renal Hemodynamics*

Group I Dog Number	Mean Blood Pressure mm. Hg				Glomerular Filtration Rate ml./min.				Renal Plasma Flow ml./min.				Renal Blood Flow ml./min.				Hematocrit			
	C	D_1	D_2	D_3	C	D_1	D_2	D_3	C	D_1	D_2	D_3	C	D_1	D_2	D_3	C	D_1	D_2	D_3
1 Hyp	124	90	93	97	49	34	31	28	163	133	92	63	320	266	184	129	49	50	50	51
2 Hyp	135	125	122	116	32	14	1	0	76	33	2	1	113	54	3	1	33	39	36	30
3 Hyp	154	155	142	121	17	9	14	10	47	21	32	21	75	35	52	36	37	40	39	42
4 Hyp	78	58	52	46	46	25	18	16	125	92	63	47	187	133	91	66	33	31	31	29
5 Hyp	121	88	72	68	31	24	15	19	138	146	95	88	226	265	173	160	39	45	45	45
6 Hyp	81	85	84	77	22	16	11	7	70	50	30	17	117	81	47	26	40	38	36	35
7 Hyp	106	95	70	75	25	17	9	10	61	40	19	27	100	59	28	39	39	33	32	30
8 Hyp	115	89	123	92	29	3	3	2	129	57	13	4	202	84	19	7	36	32	32	39
9 Hyp	113	112	103	84	69	47	39	9	253	140	93	19	395	222	190	32	36	37	51	40
Mean	114	100	96	86	36	21	16	11	118	79	49	32	193	133	87	55	38	38	39	38
% of Control		88	84	75		58	44	31		67	42	27		69	45	28		100	103	100
P Value‡		.05	.05	.001		.001	.001	.01		.05	.01	.01		.05	.001	.01		NS	NS	NS

Key to abbreviations:

C = Control observations—average of 3–10 minute periods.
D_1 = Observations made at 90° F. (32.2° C.), average of 2–10 minute periods.
D_2 = Observations made at 85° F. (29.4° C.), average of 2–10 minute periods.
D_3 = Observations made at 80° F. (26.7° C.), average of 2–10 minute periods.
NS = P > 0.10.

‡ $P - t = \bar{x}\sqrt{\frac{n(n-1)}{Sx^2}}$.

establishment of normothermia in an attempt to estimate functional alterations during hypothermia and to evaluate any residual effect on the kidney immediately after the return of the body temperature to the control levels.

Group III consisted of 19 animals in which the response to vasopressor agents during hypothermia was observed. These observations were then compared to the normothermic state in all but five of the animals. During the administration of norepinephrine, the blood pressure was returned to approximately control values. This was not always possible because of the unresponsiveness of some of the dogs. The reason for this study was that during the hypothermic state, many of the animals showed a rather marked hypotension. Since glomerular filtration rate and renal blood flow are depressed during the hypothermic state, it was thought that this may be a result of the reduction in blood pressure. Therefore, norepinephrine was administered in order to increase the blood pressure to normotensive levels in an effort to rule out the element of hypotension being responsible for the reduction in renal function. The response under these circumstances was then compared to the response following a return of the body temperature to normothermic conditions.

Group IV: The effect of hypothermia on maximum tubular absorptive capacity of glucose (TmG) was observed in six dogs. Following the control observations on renal hemodynamics the body temperature was

TABLE 1B. *Effect of Progressive Reduction of Body Temperature on Excretion of Water and Electrolytes*

Group I Dog Number	Urine Volume ml./min.				Plasma Sodium mEq./L.				Plasma Potassium mEq./L.				Urine Sodium µEq./min.				Urine Potassium µEq./min.			
	C	D_1	D_2	D_3	C	D_1	D_2	D_3	C	D_1	D_2	D_3	C	D_1	D_2	D_3	C	D_1	D_2	D_3
1 Hyp	1.4	1.2	3.2	3.0	151	152	152	171	3.3	2.3	3.0	2.5	153	101	332	344	37	29	44	39
2 Hyp	0.4	0.9	0.4	0.4	138	121	129	129	3.2	2.7	4.2	4.6	19	66	27	25	20	20	3	2
3 Hyp	0.8	1.0	1.6	1.3	144	149	149	153	3.2	2.3	2.3	2.3	32	64	123	91	11	15	29	23
4 Hyp	0.9	0.9	0.7	0.6	145	145	145	145	2.7	1.8	1.8	2.4	196	62	29	32	31	35	26	25
5 Hyp	0.4	0.7	0.6	0.7	142	144	144	144	3.1	2.3	1.7	1.7	18	50	39	61	32	22	15	18
6 Hyp	0.1	0.4	0.2	0.2	132	131	131	134	2.7	2.5	2.5	2.5	13	9	7	8	9	7	6	5
7 Hyp	0.8	2.3	1.4	1.0	131	136	136	136	2.6	3.5	2.8	2.4	19	99	127	53	23	36	20	17
8 Hyp	0.8	0.8	0.2	0.3	156	156	156	151	2.8	2.9	2.6	2.6	64	42	29	17	31	21	11	3
9 Hyp	0.7	0.4	0.3	0.2	130	130	130	130	4.6	2.9	3.1	3.2	98	45	21	7	24	32	25	7
Mean	0.7	1.0	1.0	0.9	141	140	141	144	3.1	2.6	2.7	2.7	68	60	82	71	24	24	20	15
% of Control		143	143	128		99	100	102		84	87	87		88	121	104		100	83	63
P Value‡ <		.20	.30	.40		.50	.50	.30		.20	.10	.20		.50	.50	.50		.50	.40	.10

C, D_1, D_2, and D_3—see Table 1A for key to abbreviations.

‡ $P - t = \bar{x}\sqrt{\frac{n(n-1)}{Sx^2}}$; $P > 0.10$ is not statistically significant.

reduced to 26.7° C. (80° F.) and the observations were repeated immediately. Observations could not be made over prolonged periods of hypothermia because of the renal effect of dehydration resulting from the high blood sugar levels required by the procedure.

Female dogs were used throughout this study. The dogs were hydrated with water, 40 ml./Kg. of body weight, by mouth prior to the study. Forty-five minutes later, they were anesthetized with pentobarbital (30 mg./Kg. body weight) given intravenously. Creatinine was used to measure glomerular filtration rate (GFR), para-aminohippurate (PAH) for renal plasma flow (RPF), and glucose for measuring maximum tubular function (TmG). The control observations consisted of three consecutive ten minute collection periods. Subsequent observations during hypothermia, as recorded in the tables, consist of an average of two consecutive ten minute collection periods. The temperature was reduced with an electrically controlled, water cooled hypothermic blanket (Term-O-Rite apparatus). Finally, the observations were subjected to detailed statistical analysis * as recorded in Table 1A to 3C.

Clinical Observations. Observations on the effect of hypothermia, renal hemodynamics, and excretion of water and electrolytes were made on eight male and three female patients. Glomerular filtration rate, renal blood flow, mean blood pressure, excretion of water and electrolytes were studied. Inulin was used to determine glomerular filtration rate and para-aminohippurate to determine renal plasma flow. Mean blood pressure was derived from

* Statistical analysis by R. A. Seibert.

TABLE 2A. *Effect of Hypothermia (80° F.) for 30 Minutes to 2 Hours Followed by Normothermia*

Dog Number	Mean Blood Pressure mm. Hg				Glomerular Filtration Rate ml./min.				Renal Plasma Flow ml./min.				Renal Blood Flow ml./min.				Hematocrit			
	C	D_3	D_4	D_6	C	D_3	D_4	D_6	C	D_3	D_4	D_6	C	D_3	D_4	D_6	C	D_3	D_4	D_6
Group II	Subgroup 2A—Effect of Prolonged Hypothermia Followed by Return of Body Temperature to Normal																			
10 Hyp	118	82	91	115	28	15	23	42	117	63	68	122	177	102	100	207	34	38	32	41
11 Hyp	132	77	73	114	55	18	22	40	172	32	52	124	269	54	84	230	36	41	38	46
12 Hyp	130	60	50	115	58	18	16	39	143	87	66	129	238	153	114	215	40	43	42	40
13 Hyp	79	86	78	107	91	34	32	53	262	106	78	154	391	200	144	275	33	47	46	44
14 Hyp	106	69	66	102	29	12	9	21	131	42	27	69	234	78	54	130	44	46	50	47
15 Hyp	116	68	70	85	35	10	10	17	92	32	27	69	146	64	54	135	37	50	50	49
16 Hyp	110	88	84	98	43	1	20	33	133	10	49	85	208	19	89	147	36	47	45	42
17 Hyp	157	85	100	150	42	14	18	17	120	43	49	51	226	80	91	94	47	46	46	46
18 Hyp	125	110	117	113	56	25	26	37	194	56	55	134	313	93	90	220	38	40	39	39
19 Hyp	131	60	65	140	46	8	13	34	235	41	61	158	379	61	102	255	38	33	40	38
Mean	120	79	79	114	48	16	19	33	160	51	53	110	258	90	92	191	38	43	43	43
% of Control		66	66	95		33	40	69		32	33	69		35	36	74		113	113	113
P Value‡ <		.001	.001	.30		.001	.001	.01		.001	.001	.001		.001	.001	.01		.05	.05	.05
	Subgroup 2B—Effect of Hypothermia Followed by Immediate Increase in Body Temperature to Normal																			
20 Hyp	81	70	—	100	25	11	—	17	99	39	—	55	132	64	—	87	25	39	—	37
21 Hyp	141	92	—	124	38	16	—	25	141	56	—	83	239	95	—	141	41	41	—	41
22 Hyp	106	91	—	109	56	18	—	27	193	47	—	72	311	81	—	138	38	42	—	48
23 Hyp	105	87	—	113	43	16	—	28	118	39	—	72	197	67	—	138	40	42	—	48
1 Hyp	124	97	—	166	49	28	—	43	163	63	—	97	320	129	—	211	49	51	—	54
4 Hyp	78	46	—	89	46	16	—	24	125	47	—	81	187	66	—	125	33	29	—	35
5 Hyp	121	68	—	125	31	19	—	36	138	88	—	147	226	160	—	241	39	45	—	39
24 Hyp	94	30	—	97	37	2	—	18	66	11	—	62	106	17	—	100	38	35	—	38
7 Hyp	106	75	—	119	25	10	—	16	61	27	—	38	100	39	—	51	39	30	—	26
8 Hyp	115	92	—	92	29	2	—	17	129	4	—	35	202	7	—	51	36	39	—	31
3 Hyp	154	121	—	170	17	10	—	22	47	21	—	42	75	36	—	81	37	42	—	48
Mean‡‡	116	79		116	42	14		29	137	45		89	223	79		156	38	41		42
% of Control		68		100		33		69		33		65		35		70		108		111
P Value‡ <		.001		.30		.001		.01		.001		.01		.001		.01		.30		.30

TABLE 2A—*Continued*

Dog Number	Mean Blood Pressure mm. Hg				Glomerular Filtration Rate ml./min.				Renal Plasma Flow ml./min.				Renal Blood Flow ml./min.				Hematocrit			
	C	D_3	D_4	D_6	C	D_3	D_4	D_6	C	D_3	D_4	D_6	C	D_3	D_4	D_6	C	D_3	D_4	D_6
Subgroup 2C—Effect of Hypothermia Only																				
25 Hyp	132	100			43	19			201	87			372	161			46	46		
26 Hyp	124	91			39	19			122	39			203	65			40	40		
27 Hyp	137	80			47	20			169	53			302	95			44	44		
28 Hyp	132	88			47	25			122	26			194	41			37	36		
29 Hyp	135	87			48	18			192	53			325	90			41	41		
30 Hyp	139	78			63	21			196	43			392	86			50	50		
31 Hyp	145	100			34	11			112	34			190	58			41	41		
32 Hyp	128	84			57	5			103	9			172	19			40	53		
33 Hyp	144	70			37	8			98	29			161	49			39	41		
6 Hyp	81	77			22	7			70	17			117	26			40	35		
Mean*	120	81			42	15			138	43			229	76			39	42		
% of Control		68				36				31				33				108		
P Value‡ <		.001				.001				.001				.001				.50		

Key to abbreviations:

C = Control observations (average of 3–10 minute periods).
D_3 = Observations made at 80° F. (26.7° C.) immediately after temperature reduction (average of 2–10 minute periods).
D_4 = Observations on Dogs Numbers 19 through 28 made after 1 hour of hypothermia (average of 2–10 minute periods).
D_6 = Observations made after body temperature increased back to 98° F. (37° C.) (average of 2–10 minute periods).

‡‡ Mean values for both Subgroups 2A and 2B combined.
* Mean values for 3 Subgroups (2A, 2B and 2C).
‡ See Table 1A.

TABLE 2B. *Effect of Hypothermia for 30 Minutes to 2 Hours (on Excretion of Water and Electrolytes) Followed by Normothermia*

Group II Dog Number	Urinary Volume cc./min.				Plasma Sodium mEq./L.				Plasma Potassium mEq./L.				Urinary Sodium μEq./min.				Urinary Potassium μEq./min.			
	C	D_3	D_4	D_6	C	D_3	D_4	D_6	C	D_3	D_4	D_6	C	D_3	D_4	D_6	C	D_3	D_4	D_6
10 Hyp	0.4	1.1	1.1	0.9	129	129	124	124	3.0	2.3	2.2	2.8	35	156	80	36	21	23	20	30
11 Hyp	0.8	0.6	0.8	1.0	127	127	127	124	2.9	1.9	2.3	2.3	80	25	40	14	44	17	17	21
12 Hyp	1.1	0.3	0.3	0.9	130	127	130	125	2.4	2.6	2.3	3.6	24	11	11	34	14	10	5	29
13 Hyp	0.8	1.1	1.5	0.8	128	128	128	135	3.4	2.2	3.1	2.9	21	90	107	14	26	20	22	14
14 Hyp	0.7	0.5	0.4	1.3	140	141	140	145	2.5	1.8	2.2	2.6	5	6	5	43	14	9	5	15
15 Hyp	0.5	0.5	0.9	0.9	132	133	133	136	4.0	3.7	2.3	3.2	14	25	70	21	6	12	13	45
16 Hyp	0.4	0.1	0.8	1.0	142	153	148	147	3.8	4.5	2.8	3.4	39	5	43	26	27	1	12	33
17 Hyp	0.5	0.6	0.6	0.6	146	148	148	134	3.3	2.3	2.1	2.9	11	67	51	28	20	12	14	12
18 Hyp	1.1	2.0	2.4	2.9	131	136	139	130	2.8	2.2	2.6	2.5	43	115	106	191	42	36	24	32
19 Hyp	0.7	0.3	0.4	1.4	146	144	152	151	2.8	2.3	2.2	2.9	78	11	25	60	29	4	11	33
Mean	0.7	0.7	0.9	1.2	135	137	137	135	3.1	2.6	2.4	2.9	35	51	54	47	24	14	14	26
% of Control		100	129	171		101	101	100		84	77	94		146	154	134		58	58	108
P Value <		.50	.40	.10		.40	.20	.50		.05	.01	.30		.50	.40	.50		.05	.05	.50
20 Hyp	0.3	0.3	—	0.4	133	133	—	133	2.9	2.9	—	2.9	11	15	—	15	24	16	—	17
21 Hyp	0.6	0.4	—	1.6	157	143	—	140	3.9	2.9	—	3.1	32	32	—	50	11	8	—	22
22 Hyp	1.6	0.7	—	0.0	131	149	—	149	3.2	2.7	—	2.7	238	86	—	129	31	15	—	24
23 Hyp	0.5	0.4	—	0.5	150	157	—	158	4.4	2.3	—	4.3	43	23	—	18	27	14	—	25
1 Hyp	1.4	3.0	—	4.2	—	—	—	—	3.3	2.5	—	3.5	153	344	—	172	37	39	—	48
4 Hyp	0.9	0.6	—	0.8	145	145	—	145	2.7	2.4	—	3.1	196	32	—	29	31	25	—	4
5 Hyp	0.4	0.7	—	1.3	142	144	—	141	3.1	1.7	—	2.9	18	61	—	20	32	18	—	46
24 Hyp	0.4	0.2	—	1.6	141	149	—	145	3.7	2.0	—	3.7	38	7	—	114	28	1	—	16
7 Hyp	0.8	1.0	—	2.3	131	136	—	142	2.6	2.4	—	2.9	19	53	—	84	23	17	—	30
8 Hyp	0.8	0.3	—	1.1	156	151	—	154	2.8	2.6	—	2.9	64	17	—	43	31	3	—	14
3 Hyp	0.8	1.3	—	1.4	144	153	—	155	3.2	2.3	—	5.1	32	91	—	45	11	23	—	53
Mean	0.7	0.8		1.3	139	141		141	3.2	2.5		3.2	57	61		56	25	15		27
% of Control		114		186		101		101		78		100		107		98		60		108
P Value <		.50		.10		.30		.40		.01		.50		.50		.50		.05		.50

TABLE 2B—*Continued*

Dog Number	Urinary Volume cc./min.				Plasma Sodium mEq./L.				Plasma Potassium mEq./L.				Urinary Sodium μEq./min.				Urinary Potassium μEq./min.			
	C	D_3	D_4	D_6	C	D_3	D_4	D_6	C	D_3	D_4	D_6	C	D_3	D_4	D_6	C	D_3	D_4	D_6
25 Hyp	0.8	0.8			149	149			2.9	2.5			124	102			28	12		
26 Hyp	1.9	1.3			155	155			2.8	4.9			230	108			36	25		
27 Hyp	1.9	1.5			140	146			2.5	2.1			120	131			36	15		
28 Hyp	3.3	2.3			141	141			3.6	3.6			398	191			43	17		
29 Hyp	1.7	1.1			138	138			2.5	2.7			214	87			20	12		
30 Hyp	1.3	1.5			139	144			3.7	1.9			103	130			26	13		
31 Hyp	0.8	1.4			139	139			3.0	3.1			50	170			17	22		
32 Hyp	0.7	0.4			144	144			4.4	3.7			192	90			66	30		
33 Hyp	0.6	0.3			127	128			2.9	1.9			57	5			27	3		
6 Hyp	0.1	0.2			132	134			2.7	2.5			13	8			9	5		
Mean	0.9	0.8			140	141			3.2	2.6			87	74			27	15		
% of Control		89				101				81				85				56		
P Value <		.30				.50				.50				.20				.01		

Key to abbreviations—see Table 2A.

auscultatory systolic and diastolic pressures by adding one-third of the pulse pressure to the diastolic pressure. Determinations of potassium and sodium were made using a Beckman flame photometer. Methods and technics have been described previously.[3, 5, 6] Following three ten-minute control periods the patients were anesthetized. After the induction of anesthesia, two ten-minute collection periods were again made. Then, hypothermia was induced using an electrically controlled, hypothermic blanket just as was done for the laboratory studies. The temperature was reduced to a maximum of 29° C. (Patient S. C.). Observations were recorded at the point of maximum reduction in temperature in these patients (Period D2) and also at a variable point somewhat above this point of maximum hypothermia (Tables 4A and 4B). Observations made following anesthesia and during hypothermia were then subjected to statistical analysis and compared with control values.

RESULTS

Laboratory Observations. In Tables 1A and 1B are detailed the effects of progressive reduction of body temperature on renal hemodynamics and on excretion of water and electrolytes. It will be noted that as the body temperature is progressively reduced to 27° C., there is a progressive reduction in mean blood pressure from an average of 114 mm. Hg for the control values to 86 mm. Hg ($P < 0.001$). This represents a 25% reduction in mean blood pressure. Associated with the reduction in blood pressure, there was a marked reduction in glomerular filtration rate from an average of 36 ml. per minute to 11 ml. per minute ($P < 0.01$). This represents a reduction of 69% (31% of the control value).

Associated with the reduction in glomerular filtration rate there was a parallel reduction in renal blood flow to 28% of the control values ($P < 0.01$). The hematocrit was not affected. The depression in renal

TABLE 3A. *Renal Hemodynamic Response to Increasing the Blood Pressure with Norepinephrine and a Comparison to the Response to Returning the Temperature to Normal*

Group III Dog Number	Mean Blood Pressure mm. Hg				Glomerular Filtration Rate ml./min.				Renal Plasma Flow ml./min.				Renal Blood Flow ml./min.				Hematocrit			
	C	D_3	D_5	D_6	C	D_3	D_5	D_6	C	D_3	D_5	D_6	C	D_3	D_5	D_6	C	D_3	D_5	D_6
1 Hyp	124	97	176	166	49	28	17	43	163	63	44	97	320	129	90	211	49	51	51	54
3 Hyp	154	121	151	170	17	10	10	22	47	21	19	42	75	36	33	81	37	42	42	48
4 Hyp	78	46	80	89	46	16	13	24	125	47	30	81	187	66	46	125	33	29	35	35
5 Hyp	121	68	68	125	31	19	17	36	138	88	70	147	226	160	127	241	39	45	45	39
6 Hyp	81	77	90	‡	22	7	2	‡	70	17	4	‡	117	26	6	‡	40	35	36	‡
7 Hyp	106	75	107	119	25	10	9	16	61	27	26	38	100	39	36	51	39	30	27	26
8 Hyp	115	92	95	92	29	2	3	17	129	4	18	35	202	7	27	51	36	39	34	31
10 Hyp	118	82	133	115	28	15	24	42	117	63	70	122	177	102	109	207	34	38	36	41
11 Hyp	132	77	121	114	55	18	25	40	172	32	64	124	269	54	112	230	36	41	43	46
12 Hyp	130	60	90	115	58	18	8	39	143	87	33	129	238	153	56	215	40	43	41	40
13 Hyp	79	86	100	107	91	34	13	53	262	106	29	154	391	200	51	275	33	47	43	44
14 Hyp	106	69	107	102	29	12	2	21	131	42	9	69	234	78	15	130	44	46	40	47
15 Hyp	116	68	90	85	35	10	4	17	92	32	8	69	146	64	16	135	37	50	49	49
16 Hyp	110	88	103	—	43	1	20	—	133	10	45	—	208	19	85	—	36	47	47	—
19 Hyp	131	60	65	140	46	8	13	34	235	41	61	158	379	61	102	255	38	33	40	38
23 Hyp	105	87	140	113	43	16	13	28	118	39	31	72	197	67	54	138	40	42	43	48
29 Hyp	135	87	112	—	48	18	19	—	192	53	53	—	325	90	110	—	41	41	52	—
32 Hyp	120	84	119	—	57	5	26	—	103	9	60	—	172	19	128	—	40	53	53	—
33 Hyp	144	70	135	—	37	8	11	—	98	29	61	—	161	49	109	—	39	41	44	—
Mean	116	79	110	118	42	13	13	31	133	43	39	96	217	75	69	168	38	42	42	42
% of Control		68	95	102		31	31	74		32	29	72		35	32	77		111	111	111
P Value* <		.001	.40	.50		.001	.001	.05		.001	.001	.001		.001	.001	.01		.10	.05	.05
P Value** <			.001	.001			.50	.001			.50	.001			.50	.001			.50	.50

Key to abbreviations:

C = Control observations—average of 3–10 minute periods at normotensive levels.
D_3 = Observations at 80° F. (27.7° C.) for variable periods of time—average of 2–10 minute periods.
D_5 = Observations during blood pressure elevation with norepinephrine infusion during hypothermia—average of 2–10 minute periods.
D_6 = Observations after body temperature increased to 98° F. (37° C.).

‡ Dog died during infusion of norepinephrine.
* Statistical analysis using control observations for comparison.
** Statistical analysis using Period D_3 (hypothermia) for comparison.

TABLE 3B. *Effect of Blood Pressure Elevation with Norepinephrine on Excretion of Water and Electrolytes During Hypothermia*

Group III Dog Number	Urinary Volume cc./min.				Plasma Sodium mEq./L.				Plasma Potassium mEq./L.				Urinary Sodium μEq./min.				Urinary Potassium μEq./min.			
	C	D_3	D_5	D_6	C	D_3	D_5	D_6	C	D_3	D_5	D_6	C	D_3	D_5	D_6	C	D_3	D_5	D_6
1 Hyp	1.4	3.0	1.0	4.2	—	—	—	—	3.3	2.5	5.4	3.5	153	344	103	172	37	39	27	48
3 Hyp	0.8	1.3	1.1	1.4	144	153	150	155	3.2	2.3	3.1	5.1	32	91	86	45	11	23	21	53
4 Hyp	0.9	0.6	0.7	0.8	145	145	145	145	2.7	2.4	3.3	3.1	196	32	43	29	31	25	25	42
5 Hyp	0.4	0.7	0.7	1.3	142	144	144	141	3.1	1.7	1.7	2.9	18	61	51	20	32	18	17	46
6 Hyp	0.1	0.2	0.2	‡	132	134	134	‡	2.7	2.5	3.5	‡	13	8	7	‡	9	5	2	‡
7 Hyp	0.8	1.0	0.9	2.3	131	136	142	142	2.6	2.4	2.9	2.9	19	53	31	84	23	17	12	30
8 Hyp	0.8	0.3	1.1	1.1	156	151	153	154	2.8	2.6	2.9	2.9	64	17	98	43	31	3	12	14
10 Hyp	0.4	1.1	1.5	0.9	129	129	124	124	3.0	2.3	2.2	2.8	35	156	137	36	21	23	24	30
11 Hyp	0.8	0.6	1.0	1.0	127	127	127	124	2.9	1.9	2.1	2.3	80	25	41	14	44	17	18	21
12 Hyp	1.1	0.3	0.2	0.9	130	127	130	125	2.4	1.6	4.5	3.6	24	11	9	34	14	10	1	29
13 Hyp	0.8	1.1	0.7	0.8	128	128	134	135	3.4	2.2	2.4	2.9	21	90	45	14	26	20	11	14
14 Hyp	0.7	0.5	0.3	1.3	140	141	145	145	2.5	1.8	3.9	2.6	5	6	6	43	14	9	1	15
15 Hyp	0.5	0.5	0.3	0.9	132	133	133	136	4.0	3.7	2.2	3.2	14	25	26	21	6	12	4	45
16 Hyp	0.4	0.1	0.6	—	142	153	151	—	3.8	4.5	2.9	—	39	5	37	—	27	1	11	—
19 Hyp	0.7	0.3	0.4	1.4	146	144	152	151	2.8	2.3	2.2	2.9	78	11	25	60	29	4	11	33
23 Hyp	0.5	0.4	0.3	0.5	150	157	157	158	4.4	2.3	2.7	4.3	43	23	26	18	27	14	10	25
29 Hyp	1.7	1.1	1.0	—	138	138	140	—	2.5	2.7	2.3	—	214	87	74	—	20	12	12	—
32 Hyp	0.7	0.4	0.8	—	144	144	144	—	4.4	3.7	3.7	—	192	90	54	—	66	30	21	—
33 Hyp	0.6	0.3	0.5	—	127	128	130	—	2.9	1.9	1.9	—	57	5	17	—	27	3	11	—
Mean	0.7	0.7	0.7	1.3	138	140	141	141	3.1	2.5	2.9	3.2	68	60	48	45	26	15	13	32
% of Control		100	100	186		101	102	102		81	94	103		88	71	66		58	50	123
P Value*		.50	.50	.05		.05	.01	.10		.001	.50	.50		.50	.30	.50		.01	.001	.20
P Value**			.50	.01			.20	.10			.05	.001			.50	.20			.30	.001

Key to abbreviations—see Table 3A for C, D_3, D_5 and D_6.

* Statistical analysis using control observations for comparison.

** Statistical analysis using Period D_3 (hypothermia) for comparison.

TABLE 4A. *Renal Hemodynamic Response to Hypothermia in Man*

	Mean Blood Pressure mm. Hg				Glomerular Filtration Rate ml./min.				Renal Plasma Flow ml./min.				Renal Blood Flow ml./min.				Hematocrit				Temperature	
Patient	C	AN	D_1	D_2	C	AN	D_1	D_2	C	AN	D_1	D_2	C	AN	D_1	D_2	C	AN	D_1	D_2	D_1	D_2
1. B. H.	99	93	94	102	86	78	81	64	521	449	341	197	868	748	568	328	40	40	40	40	31.4	30.0
2. A. J.	99	72	75	77	100	99	71	65	715	675	638	426	1459	1378	1418	991	51	51	55	57	32.2	30.0
3. P. M.	70	70	70	77	88	59	50	50	417	205	226	221	772	380	435	442	46	46	48	50	35.0	32.2
4. C. H.	130	147	130	123	110	71	74	55	857	384	384	321	1453	640	640	553	41	40	40	42	33.9	32.2
5. G. P.	73	70	77	77	101	81	70	71	575	622	370	322	1065	1131	673	631	46	45	45	49	34.4	32.2
6. S. P.	77	77	52	73	82	102	84	99	533	734	618	523	1006	1385	1261	1067	47	47	51	51	32.8	29.4
7. H. H.	120	107	90	92	70	90	52	56	484	508	290	397	834	876	483	662	42	42	40	40	33.9	32.2
8. D. J.	103	97	—	87	101	89	—	72	776	668	—	436	1411	1215	—	651	45	45	—	33	33.3	32.2
9. S. C.	132	127	125	120	97	81	49	46	457	482	209	196	802	846	354	392	43	43	41	50	31.0	29.0
10. K. W.	120	117	105	86	109	157	85	55	675	854	569	372	993	1256	948	631	32	32	40	41	33.3	31.1
11. R. N.	115	96	87	74	111	37	78	71	520	220	357	426	825	338	558	666	37	35	36	36	32.8	30.0
Mean	103	98	91	90	96	86	69	64	594	527	400	349	1044	927	734	638	43	42	44	44		
% of Control		95	88	87		90	72	67		89	67	59		89	70	61		98	102	102		
P Value*		.20	.05	.05		.40	.001	.001		.40	.05	.001		.30	.05	.001		.50	.40	.30		
P Value**			.05	.10			.20	.10			.05	.001			.05	.01			.10	.20		

Key to abbreviations:

C = Control observations (average of 3–10 minute periods).
AN = Observations after the induction of anesthesia (average of 2–10 minute periods).
D_1 = Observations after initial reduction in body temperature (average of 2–10 minute periods).
D_2 = Observations after maximum reduction in body temperature (average of 2–10 minute periods).

* Statistical analysis using control observations for comparison.
** Statistical analysis using Period An (after induction of anesthesia) for comparison.

TABLE 4B. *Effect of Hypothermia on Excretion of Water and Electrolytes in Man* ‡

Patient	Urinary Volume cc./min.				Plasma Sodium mEq./L.				Plasma Potassium mEq./L.				Urinary Sodium µEq./min.				Urinary Potassium µEq./min.				Age
	C	AN	D_1	D_2	C	AN	D_1	D_2	C	AN	D_1	D_2	C	AN	D_1	D_2	C	AN	D_1	D_2	
1. B. H.	0.4	0.5	1.0	2.9	149	148	147	154	5.9	5.9	4.5	4.5	83	85	188	415	42	40	31	49	60
2. A. J.	0.4	0.4	2.5	2.2	134	139	137	137	4.4	4.4	4.1	3.0	135	134	172	68	43	50	16	22	42
3. P. M.	0.5	0.4	0.1	0.7	144	152	157	157	3.0	3.0	3.0	2.4	93	51	54	32	83	34	25	47	56
4. C. H.	1.1	1.5	3.9	4.8	150	154	154	154	3.6	5.0	5.0	4.0	148	136	136	65	63	30	17	15	51
5. G. P.	0.4	0.4	2.3	2.3	150	150	150	150	3.6	3.2	2.7	2.3	54	47	30	37	27	37	21	14	41
6. S. P.	0.5	0.5	0.6	1.6	151	151	148	151	4.1	4.1	3.1	3.0	94	101	49	206	34	72	35	43	44
7. H. H.	1.4	2.0	3.4	4.9	136	131	131	139	5.5	5.4	5.4	4.7	264	144	74	91	92	88	42	41	—
8. S. C.	2.0	1.4	1.3	0.7	142	143	143	144	5.1	4.7	4.6	4.3	340	265	220	232	102	91	46	37	—
9. K. W.	0.4	2.7	4.5	0.9	141	134	134	135	3.7	3.8	3.8	2.9	88	440	84	70	50	95	40	37	54
10. R. N.	4.8	4.8	8.0	4.7	139	139	138	142	4.6	4.6	4.6	3.2	101	38	83	67	78	56	36	51	52
Mean	1.2	1.5	2.8	2.6	144	144	144	146	4.4	4.4	4.1	3.4	140	144	109	128	61	59	31	36	
% of Control		125	233	217		100	100	101		100	93	77		103	78	91		97	51	59	
P Value*		.30	.05	.05		.50	.50	.10		.50	.20	.001		.50	.30	.50		.50	.01	.01	
P Value**			.01	.05			.50	.10			.10	.001			.40	.50			.001	.05	

‡ See Table 4A for key to abbreviations.
* Statistical analysis using control observations for comparison.
** Statistical analysis using Period An (after induction of anesthesia) for comparison.

function in these animals was a progressive one which paralleled the decrease in body temperature.

Although the glomerular filtration rate was markedly reduced, this was not associated with a decrease in urinary volume ($P > 0.10$) nor in a significant decrease in sodium excretion ($P > 0.10$). This is remarkable in that under normothermic conditions any manipulation that reduces the glomerular filtration rate to this extent will greatly depress urinary volume and excretion of sodium.[1,2] Excretion of potassium was depressed to a degree which approached statistical significance ($P < 0.10$). Observations on a larger number of animals in Group 2 confirmed this deduction. It would appear that the tubular enzymatic reabsorptive mechanism is depressed and therefore the reabsorption of sodium and water is apparently reduced. On the other hand, excretion of potassium by the tubules is an active process and by the same reasoning, the urinary excretion of potassium was reduced by hypothermia. There was no significant effect on plasma sodium but the plasma potassium decreased from 3.1 mEq/liter to 2.7 which was not statistically significant.

Similar to the animals in Group I, the observations in a larger group of dogs in Group II showed that the mean blood pressure for the entire group (Sub-groups 2A, 2B and 2C) was reduced to 68% of the control values at maximum hypothermia (27° C.). This was associated with a significant reduction in glomerular filtration rate ($P < 0.001$) and a parallel reduction in renal blood flow ($P < 0.001$). There were no significant alterations ($P < 0.10$) in excretion of water or sodium (Table 2B). There was a significant reduction in excretion of potassium ($P < 0.01$).

When the temperature was maintained at 26.7° C. for one hour or more (Sub-group 2A), there was not a progressive reduction in blood pressure, glomerular filtration rate or renal blood flow but instead, these functions remained constant. This indicates that the reduction in blood pressure and renal function is a direct result of the degree of hypothermia rather than being related to the period of time that the temperature remains reduced. Similar deductions can be made relative to the effect of prolonged hypothermia on urinary volume and sodium excretion in that the observations after one hour of hypothermia were similar to the observations made immediately after maximum reduction in body temperature to 26.7° C.

When the temperature was increased to normothermic levels in 19 of the animals (Sub-groups 2A and 2B), the blood pressure for the group returned to approximately the same value that existed prior to the induction of hypothermia (116 mm. Hg). However, glomerular filtration rate did not return to control values but increased only to 69% of the control values ($P < 0.01$) as contrasted to 33% of the control value during maximum hypothermia. Likewise, renal blood flow returned only to 70% of the control values ($P < 0.01$) as contrasted to 35% during maximum hypothermia. The hematocrit was not altered significantly following the increase in body temperature.

When the body temperature increased there was a moderate increase in water excretion which approached statistical significance ($P < 0.10$). The excretion of sodium after return of body temperature to normal, was 98% of the control value. The excretion of potassium returned to 108% of the control value ($P < 0.50$) as contrasted to 60% of the control during maximum hypothermia ($P < 0.05$). Concentration of sodium with plasma was not altered following a return of body temperature to the normothermic state but the plasma potassium increased from 2.5 millequivalents to 3.2 millequivalents, an increase of 22% in the normothermic state as compared to maximum hypothermia.

Referring to Table 3A, we can see that the mean blood pressure for the group of animals was increased with the infusion of norepinephrine from 79 mm. Hg to 110 mm. Hg ($P < 0.001$) which was 95% of the average control value. Despite the increase in blood presure, the depressed rate of glomerular filtration and renal blood flow were not improved ($P > 0.50$). As the mean blood pressure increased, neither urinary volume ($P > 0.50$) nor excretion of sodium ($P > 0.50$) increased. As a matter of fact, there was a slight reduction in sodium excretion following the infusion of norepinephrine from 88% of the control value for this group of animals to 71% which, however, was not statistically significant. These observations seem to indicate that the depression in renal function was not a result of the hypotension but was rather related to the hypothermic state.

When the temperature was increased to control values in this group of animals which received norepinephrine during hypothermia, the mean blood pressure increased to the control values. Although glomerular filtration rate increased as in the previous observations, it did not return to the control values, increasing ($P < 0.001$) from 31% of the control value at maximum hypothermia to 74% of the control values after the temperature was increased to normothermic levels. There was a parallel increase in renal blood flow ($P < 0.001$) to 77% of the control values after return of body temperature to normal as contrasted to 35% during maximum hypothermia. The increase in glomerular filtration rate was associated with an increase in urinary volume from .7 ml. per minute to 1.3 ($P < 0.01$) after the return of body temperature to normal. This was not associated with a parallel increase in sodium excretion ($P < 0.20$). However, potassium increased ($P <$

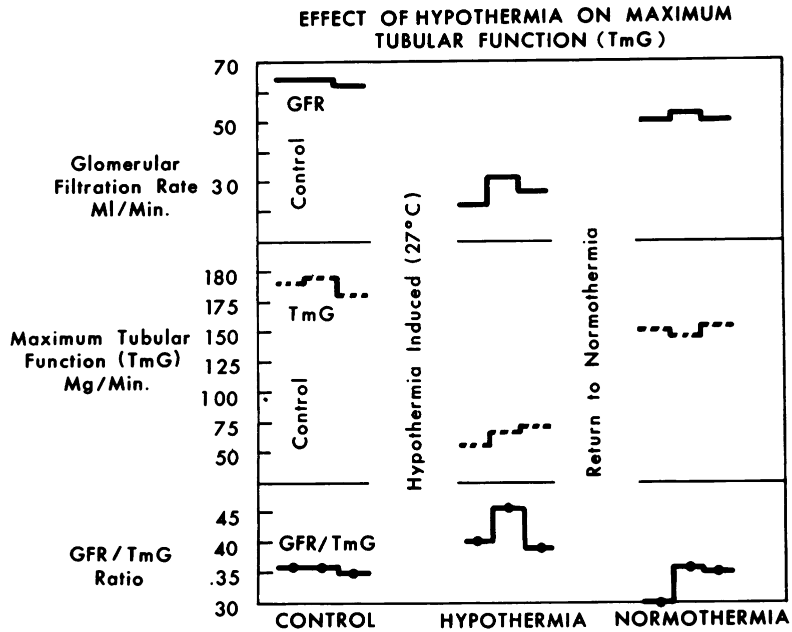

FIG. 1. Effect of hypothermia (80° F.) on maximum tubular function (TmG). As the temperature is reduced there is a concurrent reduction in glomerular filtration rate (GFR) and maximum tubular function (TmG). Frequently the latter is depressed more than the former. When normothermia is re-established both GFR and TmG return toward, but not entirely to normal.

0.001) from 58% of the control values at maximum hypothermia to 123% after the normothermic state was induced.

As rate of glomerular filtration and renal blood flow decreased during hypothermia there was a parallel reduction in maximum tubular function (Figs. 1 and 2) to 30% of control value for the group. Usually the GFR/TmG ratio increased due to a somewhat greater reduction in maximum tubular function than in glomerular filtration rate, apparently a result of enzymatic inhibition.

Observations in Man. The observations in man parallel the observations made in the laboratory. As anesthesia was induced, there was frequently a slight reduction in mean blood pressure. Then as the temperature decreased there was usually an additional reduction in mean blood pressure ($P < 0.05$) which was marked in only one instance (Patient S.P.—Table 4A). The average mean blood pressure for the group decreased from 98 mm. Hg to 91 mm. Hg ($P < 0.05$). This was associated with a significant reduction in glomerular filtration rate (67% of control), comparing the control values to the hypothermic values. However, this was partly due to anesthesia.

The renal blood flow paralleled the rate of glomerular filtration but the depression was more marked. Anesthesia did not appear to have a significant effect on renal blood flow ($P < 0.30$). However, when the observations during hypothermia are compared with the pre-anesthesia observations, the changes were significant ($P < 0.001$), as were the changes when the observations during anesthesia but before hypothermia were used for comparison ($P < 0.01$). Hypothermia did not appear to affect the hematocrit. This again was quite similar to the results observed in the laboratory animal. Excretion of sodium was not altered significantly and excretion of potassium decreased ($P < 0.05$). Although the concentration of sodium in the plasma was not

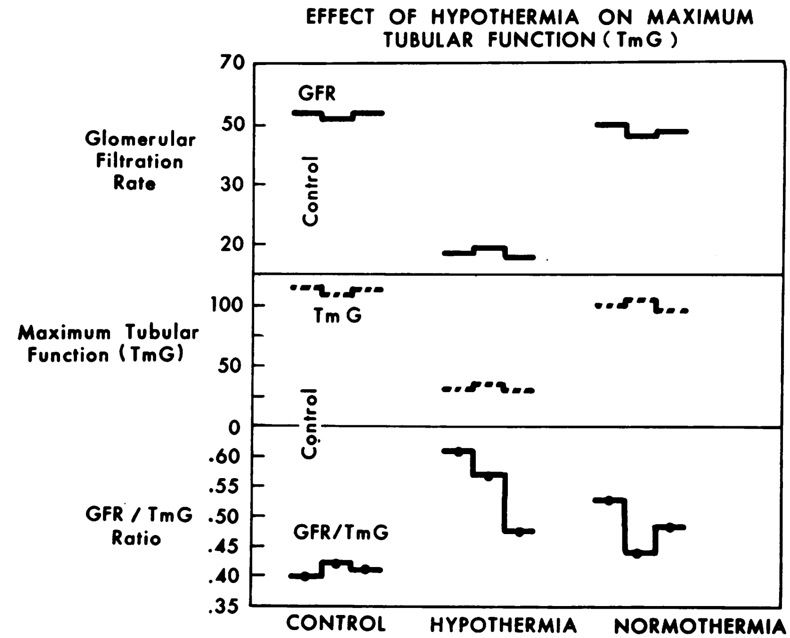

FIG. 2. Effect of hypothermia on maximum tubular function. The response was similar to that observed in Figure 1.

altered, the concentration of potassium decreased ($P < 0.001$), which may have been due (at least in part) to the intravenous infusion of fluids.

DISCUSSION

The observations in the current study indicate that alterations in renal hemodynamics and excretion of water and electrolytes in laboratory animals (dogs) due to hypothermia are quite similar to alterations produced by this procedure in man. As the body temperature is reduced, there is a progressive reduction in mean blood pressure. This is associated with a reduction in rate of glomerular filtration and renal blood flow. Despite the reduction in glomerular filtration rate, the excretion of water and sodium is not altered significantly. This is apparently due to a depression in tubular transport of these substances. Therefore, despite the reduction in glomerular filtration rate, which would usually be associated with a marked reduction in excretion of water and sodium, this does not occur during the hypothermic state. At the same time, excretion of potassium is sharply reduced during hypothermia, probably due to the fact that its excretion is partly dependent on tubular excretion. With the depression of enzymatic processes in the renal tubule, this retrograde excretion may be depressed. On the other hand, the level of plasma potassium was reduced slightly during the hypothermic state which may or may not be partly responsible for the reduction in excretion of potassium by the kidney. These observations during the hypothermia are in contrast to the response when glomerular filtration rate is reduced under normothermic conditions. When this occurs there is a marked reduction in sodium and water excretion [1, 2, 3, 7, 8] associated with the reduction in glomerular filtration rate. Under the latter circumstances, tubular enzymatic processes are entirely normal. As a consequence, when rate of glomerular filtration is reduced, tubular reabsorption continues which results in a retention of sodium and water. Excretion of potassium is also depressed but in the latter instance this probably results from inadequate urinary output.

SUMMARY AND CONCLUSIONS

The effect of hypothermia on renal hemodynamics and on excretion of water and electrolytes has been studied on 39 dogs and 11 human subjects in whom the hypothermia was used to facilitate vascular operations. There was essentially no difference between the laboratory observations and those made on the human subjects.

As the body temperature was progressively reduced to 27° C. (laboratory observations), the mean blood pressure decreased progressively to approximately 75% of the control values. This was associated with a progressive reduction in glomerular filtration rate and renal blood flow without significant alterations in urine or sodium excretion.

The reduction in rate of glomerular filtration and in renal blood flow was not improved when the blood pressure was raised to control values with an infusion of norepinephrine. However, when the body temperature was again increased to the control levels, the mean blood pressure returned completely to the control levels although the glomerular filtration rate and renal blood flow usually returned to only about 75% of the control levels. However, within 24 hours, these had returned to the control levels in those animals studied. There was essentially no difference in these responses between dogs and man.

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