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Effects of Plasma Electrolyte Abnormalities on Total Peripheral Resistance and other Hemodynamic Parameters in Dogs (38043)

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A recent study from our laboratory demonstrated that acute, generalized plasma electrolyte abnormalities were associated with changes in mean, systolic and diastolic blood pressures in the dog (1, 2). Hypo-osmolarity, hypomagnesemia, hypokalemia, hypercalcemia, and alkalosis, singly or in various combinations, produced increases in systemic blood pressures. The greatest increase occurred when these abnormalities were produced simultaneously. However, the most striking and the most significant blood pressure change occurred during the combination of hyperkalemia, hypermagnesemia, hyperosmolarity, hypocalcemia and acidosis (1). In this situation, mean blood pressure fell 19% during the combined abnormalities; the response was enhanced to a 35% pressure decrease when the same abnormalities were created in dogs with their neurological barostatic system rendered inoperable (3).

The mechanism of the altered blood pressure could be through alterations of either or both of the two direct determinants of arterial blood pressure, viz, cardiac output or total peripheral resistance.

It is well established that local, small, acute plasma electrolyte abnormalities alter vascular resistance in most organs studied (4–9), and, as shown by Mellander's group (10), hyperosmolarity is a particularly potent dilator in intact and isolated vascular smooth muscle. Resistance changes are enhanced when two or more ionic abnormalities are created simultaneously in isolated organs (8). It is also well known that acute, local electrolyte abnormalities affect myocardial contractile force (11–16).

The present study was undertaken to determine the involvement of total peripheral resistance in the arterial blood pressure responses during single and multiple plasma electrolyte abnormalities in the intact dog. Experiments were also carried out in animals whose neurological barostatic mechanisms were rendered inoperable, thus allowing demonstration of any effects of the abnormalities on total peripheral resistance without the influence of compensatory reactions mediated through the autonomic nervous system.

Materials and Methods. A total of 129 experiments was completed in 102 adult mongrel dogs of both sexes weighing an average of 15 kg (range 13–20 kg). All animals were anesthetized with 30 mg/kg sodium pentobarbital and anticoagulated with 5 mg/kg sodium heparin. Depth of anesthesia was maintained by giving small, supplemental doses of sodium pentobarbital whenever a conjunctival reflex appeared. No more than three experimental procedures were carried out in any animal of this group.

The experimental setup has been described in detail previously (17). Following establishment of artificial respiration with a Harvard constant volume respirator, the chest was opened in the fourth or fifth intercostal space on the left side. The pericardium was incised and the azygos vein ligated. In 35 experiments, the superior and inferior vena cavae were cannulated with large bore, low resistance Tygon tubing near their en-

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trance to the heart. Total systemic venous return (VR) flowed by gravity into a lowered 500 cc plastic reservoir (situated in a water bath maintained at 38°C) and was returned to the cannulated right atrium with a pressure independent Sigmamotor pump. This extracorporeal system was primed with approximately 500 cc of heparinized fresh whole blood from a donor dog.

In another 94 experiments, the right atrium was cannulated so that all the blood from the superior and inferior vena cavae and azygous vein flowed by gravity into the previously described extracorporeal circuit. The blood was returned to the ligated and cannulated pulmonary artery by means of a pressure independent Harvard Apparatus Piston Pump.

In all experiments, cardiac inflow was held constant with the inflow pump, hence, changes in arterial pressure directly reflected changes in total peripheral resistance.

Mean systemic arterial blood pressure was recorded from a cannulated femoral artery using a Statham pressure transducer connected to a Sanborn direct writing recorder. Cardiac frequency was recorded with standard electrocardiographic leads connected to a Sanborn Cardio-Tach preamplifier. Total peripheral resistance was calculated by dividing the appropriate mean arterial blood pressure by the respective steady-state venous return. A femoral vein was cannulated (PE 240) for administration of sodium pentobarbital and heparin as required. Arterial blood samples for laboratory analysis were taken before, during and after each infusion. Plasma electrolyte concentrations were determined as follows: [Mg^{2+}] and [Ca^{2+}] by atomic absorption spectrophotometry (Perkin Elmer, Model 290B); [K^+] and [Na^+] by flame photometry (Beckman, Model 105). Plasma osmolality was determined with an advanced osmometer (freezing point depression). Arterial blood hematocrit and pH were measured with a microhematocrit centrifuge and Astrup expanded scale pH meter, respectively.

The desired single plasma electrolyte changes were induced by a 5 min infusion of the solutions shown in Table I. Predicted plasma electrolyte changes and other parameters are also shown. Infusion was into the tubing upstream to the blood inflow pump.

Similar single and multiple electrolyte abnormalities were created in spinally blocked dogs (6–8 cc procaine hydrochloride exchanged for cerebrospinal fluid intrathecally via the cisterna magna). An additional 8 experiments were carried out in spinally blocked dogs in which plasma [K^+] and [Mg^{2+}] were elevated simultaneously. Infusion of equal volumes of isotonic KCl

TABLE I. Summary of Procedures Utilized.

Procedure	Solution	Osmolarity mOsm/l	Volume cc/min	Total volume infused cc	Predicted plasma change
1	NaCl	300	1.91	9.55	None
2	NaCl	300	11.46	57.30	None
3	KCl	298	1.91	9.55	↑K^+
4	$MgCl_2$	299	1.91	9.55	↑Mg^{2+}
5	NaCl	1710	7.64	38.20	↑Osmolarity
6	KCl $MgCl_2$	300 300	1.91 1.91 3.82	19.10	↑K^+, ↑Mg^{2+}
7	KCl $MgCl_2$ NaCl	300 300 1710	1.91 1.91 7.64 11.46	57.30	↑K^+, ↑Mg^{2+} ↑Osmolarity

and $MgCl_2$ at a total rate of 3.82 cc/min raised plasma $[K^+]$ and $[Mg^{2+}]$ to similar levels as occurred when hyperkalemia or hypermagnesemia were singly induced. Following all spinal blockade procedures, a continuous infusion of approximately 10 γ/min (range 2–20 γ/min) of norepinephrine (levarterenol) was required to maintain an arterial blood pressure corresponding to the "preblocked" level.

Five minute saline control infusions at 1.91 cc/min or 11.46 cc/min in both intact and spinally blocked dogs were employed to ascertain the effects of hypervolemia and dilution on the measured parameters.

All data were subjected to a Student's *t* statistical procedure modified for paired replicate analysis, thereby allowing each experimental animal to serve as its own control. A *P* value of less than 0.05 was considered significant. Also, an in-groups paired analysis of 2 variants was employed to determine significance values for the resistance changes observed in the spinally blocked animal series.

Results. Figure 1 shows the average total peripheral resistance results of all experiments completed in this study. The left side shows data from the intact dogs and the right side shows data from spinally anesthetized (procainized) dogs. The absolute level of starting resistance was not statistically different in the two series ($P > 0.05$).

In the "unblocked" intact dogs, hyperosmolality and the combination of hyperkalemia, hypermagnesemia and hyperosmolality caused significant decreases in total peripheral resistance (TPR) of 6% and 11%, respectively ($P < 0.05$). The decrease in TPR caused by the multiple electrolyte abnormalities was significantly greater than the change caused by hyperosmolality

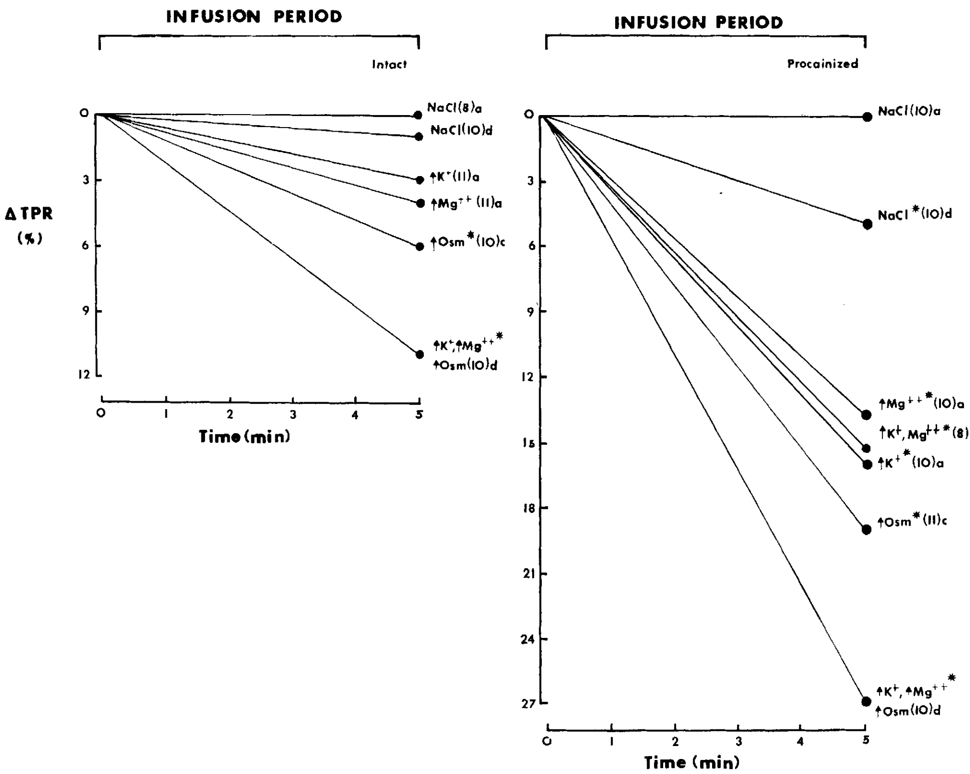

FIG. 1. Summary of responses of all groups expressed as percent change in total peripheral resistance (TPR) from control at the fifth minute of electrolyte solution infusion; left side shows intact dog series; right side shows spinally anesthetized (procainized) dog series; numbers in parentheses refer to number of experiments; * = $P < 0.05$.

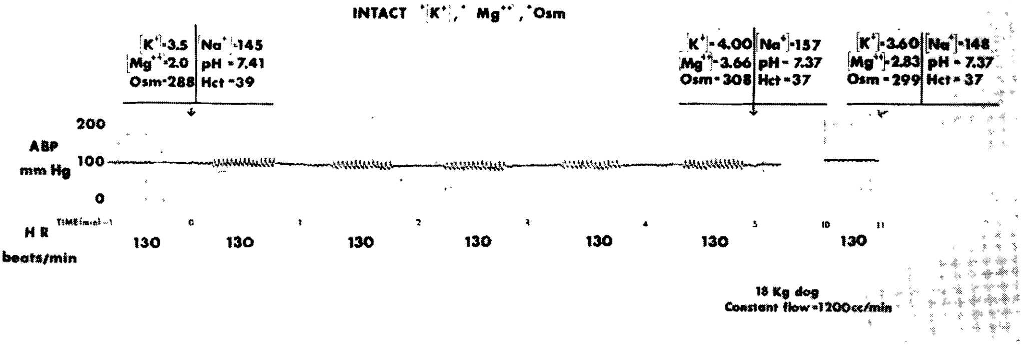

FIG. 2. Tracing of an experiment from the intact dog series showing cardiovascular effects of a five minute infusion of electrolyte solutions which created hyperkalemia, hypermagnesemia, hyperosmolarity and decreased pH. ABP = arterial blood pressure, HR = heart rate, Hct = hematocrit, Osm = osmolarity.

alone ($P < 0.05$). Hyperkalemia, hypermagnesemia or NaCl infusion (control) produced no significant change in calculated TPR ($P > 0.05$).

In the "spinally blocked" dogs, increasing plasma [Mg^{2+}] produced a significant fall in TPR of 14% when compared to its isovolemic NaCl control infusion ($P < 0.05$). Similarly, increasing plasma [K^+] and [Mg^{2+}] produced a 15% decrease in TPR when compared to the 1.91 cc/min isotonic NaCl control infusion ($P < 0.05$). The percent change in TPR due to singly increasing plasma [K^+] or [Mg^{2+}], or due to simultaneous increases in [K^+] and [Mg^{2+}] were not significantly different from one another ($P > 0.05$). Increasing plasma osmolality caused a decrease in TPR of 15% when compared to the 11.46 cc/min isotonic NaCl control infusion ($P < 0.05$). Increasing plasma [K^+], [Mg^{2+}], and osmolality simultaneously caused a significant decrease in TPR of 22% when compared to the 11.46 cc/min saline control infusion ($P < 0.05$). This change was significantly different from the percent change in TPR caused by single electrolyte abnormalities of hyperkalemia, hypermagnesemia or hyperosmolality or the combination of hyperkalemia and hypermagnesemia ($P < 0.05$).

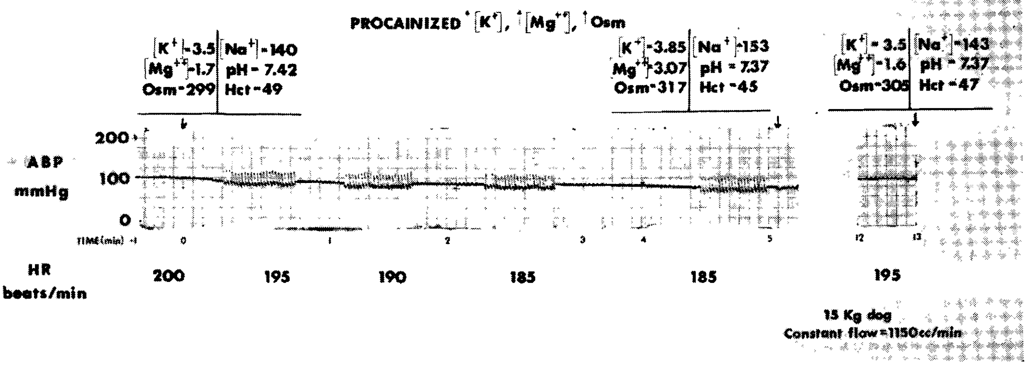

FIG. 3. Tracing of an experiment from the spinally anesthetized (procainized) dog series showing cardiovascular effects of a five minute infusion of electrolyte solutions which created hyperkalemia, hypermagnesemia, hyperosmolarity and decreased pH. ABP = arterial blood pressure, HR = heart rate, Hct = hematocrit, Osm = osmolarity.

Figure 2 shows a representative tracing of one experiment in which the simultaneous abnormalities created were hyperkalemia (+0.5 mEq/l), hypermagnesemia (+1.66 mEq/l), hyperosmolality (+20 mOsm/l) and decreased pH (−0.04 units). Hematocrit fell from 39% to 37% and plasma sodium concentration rose 12 mEq/l. Associated with these abnormalities was a decrease in mean arterial blood pressure of 10 mm Hg by the fifth minute of infusion. Calculated total peripheral resistance decreased 0.008 mm Hg/ml/min by the second minute of infusion and remained depressed throughout the infusion. Heart rate was unaffected.

Figure 3 shows a representative tracing of one experiment in a spinally anesthetized dog. The abnormalities created were hyperkalemia (+ 0.35 mEq/l), hypermagnesemia (+1.37 mEq/l), hypernatremia (+13 mEq/l) and hyperosmolality (+18 mOsm/l). Blood pH and hematocrit decreased 0.05 units and 4% (from 49% to 45%), respectively, during the infusion. Associated with these abnormalities was a progressive decrease in mean arterial blood pressure of 25 mm Hg by the end of the infusion. In this experiment, calculated total peripheral resistance progressively decreased to a maximum of 0.022 mm Hg/ml/min during the infusion.

Table II presents all of the data collected from each experimental procedure utilized in this study. Average changes in the denoted hemodynamic and measured blood parameters before (C), during (I) and after (PI) each procedure are shown. Analysis of electrolyte data shows that the predicted plasma changes were created in each instance. Note that the experimental procedures completed in the intact dogs directly precede their identical counterpart procedure carried out in spinally anesthetized (procainized) dogs.

Discussion. These studies show that acutely induced, generalized hyperosmolality and the combination of hyperkalemia, hypermagnesemia and hyperosmolality produces a fall in mean arterial blood pressure which is due to a decrease in total peripheral resistance, since cardiac inflow was held

TABLE II. Average Effects of I.V. Infusions of Test Solutions on Mean Arterial Blood Pressure, Calculated Total Peripheral Resistance, Heart Rate, and Change in Reservoir Volume and Measured Blood Parameters in Intact and Spinally Anesthetized (Procainized) Dogs.[a]

Procedure	Predicted plasma change	N	Mean blood pressure (mmHg)			Total peripheral resistance (mmHg/ml/min)			Heart rate (beats/min)			Change in reservoir volume (ml)			K^+ (mEq/l)			Mg^{2+} (mEq/l)			Na^+ (mEq/l)			Osm (mOsm/l)			pH (units)			HCT (%)		
			C	I	PI	C	I	PI	C	I	PI	C	I	PI	C	I	PI	C	I	PI	C	I	PI	C	I	PI	C	I	PI	C	I	PI
1	NONE	8	95	94	96	.08	.08	.08	140	142	141	0	−21	3	3.15	3.0	3.1	2.2	2.1	2.2	147	147	146	317	315	316	7.38	7.39	7.35	44	44	45
1**	NONE	10	99	97	96	.069	.067	.065	189	187	189	0	−44*	−63*	3.0	2.9	2.9	1.9	1.9	2.0	152	153	153	305	305	306	7.39	7.36*	7.33*	44	44	44
2	NONE	10	95	94	98	.084	.084	.087	150	150	150	0	−20	−16	3.2	2.9*	3.0*	2.2	2.1	2.1	147	148	148	313	315	315	7.38	7.36*	7.35*	41	40	42
2**	NONE	10	90	85*	91	.056	.053*	.057	185	181*	181*	0	−48*	−3	3.3	3.2	3.3	2.58	2.52	2.53	158	157	157	318	317	317	7.38	7.39	7.39	39	37	38
3	↑K^+	11	84	81	83	.070	.068	.069	151	155*	150	0	−6	−5	3.55	4.19*	3.32	2.13	2.1	2.1	146	145	146	308	308	308	7.35	7.35	7.34	39	39	39
3**	↑K^+	10	87	74*	76*	.069	.058*	.058*	190	190	190	0	−16	−33*	3.4	4.1*	3.8*	2.1	2.2	2.1	148	149	149	311	314	312	7.39	7.36	7.37	46	45	46
4	↑Mg^{2+}	11	85	82	86	.076	.072	.077	155	150*	150*	0	+9	+6	3.9	4.0	4.0	2.04	3.85*	2.72	149	150	148	301	302	301	7.35	7.35	7.35	40	40	40
4**	↑Mg^{2+}	10	92	78*	90	.064	.055*	.063	184	177*	177*	0	−17	−34	3.46	3.36	3.41	3.17	5.1*	3.89*	153	153	152	313	314	312	7.38	7.36	7.37	42	42	42
5	↑Osm	10	77	73*	76	.067	.063*	.065	150	147*	149	0	+70*	+88*	3.5	3.0*	3.0*	1.92	1.9	1.97	143	153*	148*	298	318*	308*	7.34	7.32*	7.30*	40	36*	37*
5**	↑Osm	11	83	69*	79	.059	.048*	.055	192	191	192	0	+24*	+5	3.2	2.9*	3.0	3.05	2.7	2.75	154	168*	158*	316	337*	321*	7.34	7.31*	7.32	38	36*	37
6**	↑K^+, ↑Mg^{2+}	8	92	79*	88	.062	.053*	.059	182	179	179	0	−28*	−31*	3.83	4.06*	3.52*	2.83	4.77*	3.8*	154	152	152	313	310	313	7.38	7.37	7.36	39	39	39
7	↑K^+, ↑Mg^{2+}, ↑Osm	10	81	72*	77*	.065	.058*	.062*	135	131	132	0	+105*	+119*	3.1	3.5*	3.0	1.89	3.83*	2.8*	140	148*	144*	284	306*	296*	7.38	7.33*	7.33*	41	38*	38*
7**	↑K^+, ↑Mg^{2+}, ↑Osm	10	84	61*	64*	.076	.055*	.060*	183	174*	180	0	+119*	+84*	3.2	3.6*	3.3	1.9	3.7*	2.8*	142	151*	147*	308	331*	321*	7.32	7.28*	7.29*	43	38*	40*

[a] C = control values; I = values at 5th minute of infusion; PI = values 3–7 minutes post-infusion. Values marked (*) are significant at the $P = 0.05$ level, relative to control values (C). Procedures listed correspond to those in Table I.

** = denotes procedures carried out in spinally anesthetized (procainized) dogs.

constant. These studies also indicate that mean arterial blood pressure changes in response to single and multiple electrolyte and osmolar abnormalities are partially masked by the neurological barostatic system.

Our study shows that generalized acute electrolyte and osmolar abnormalities can alter total peripheral resistance, as predicted from studies in isolated organs (4–10) and provides a mechanism responsible for at least part of the blood pressure changes seen in earlier studies from our laboratory (1, 2). However, our study gives little additional information concerning mechanisms responsible for the observed decreases in total peripheral resistance.

While the falls in resistance occur during isotonic KCl or $MgCl_2$ infusion apparently result from active dilation of vascular smooth muscle, resistance decreases associated with hyperosmolarity is more likely due to a combination of active and passive factors (18, 19). Hypertonic plasma results in loss of vascular smooth muscle water, shrinkage, and an increase in vessel caliber (10) as well as a decrease in blood viscosity due to hemodilution, both of which decrease resistance (10, 18, 19). On the other hand, hyperosmolarity causes an increase in blood viscosity by altering red blood cell deformability (20), which would tend to increase resistance, although the significance of the increase on vascular resistance is questionable (20). Additionally, these changes appear to be of relatively minor importance and the major change in resistance during hyperosmolarity is said to be dependent upon active change in vessel caliber, particularly during the steady-state (18, 19).

The current study supports the hypothesis that the fall in arterial blood pressure seen in intact dogs during hyperosmolality and the combined abnormalities of hyperkalemia, hypermagnesemia and hyperosmolality (1) is, in part, due to a decrease in total peripheral resistance. This does not, however, rule out that in the intact animal, cardiac output may also contribute to the fall in arterial blood pressure. These results also indicate that arterial blood pressure changes in response to single and multiple electrolyte abnormalities may be partially masked because of operable compensatory systems such as the neurologic barostatic mechanism.

Summary. The effects of electrolyte and water abnormalities on total peripheral resistance (TPR) were studied in anesthetized dogs. Cardiac input was maintained constant by means of a pump. A 5 min intranvenous (IV) infusion of isotonic KCl ($N = 11$) or $MgCl_2$ ($N = 11$) solution at 1.91 cc/min increased plasma $[K^+]$ by 0.64 mEq/1 and increased $[Mg^{2+}]$ by 1.83 mEq/1. These abnormalities did not significantly alter TPR. A 5 min infusion of hypertonic saline solution at 7.64 cc/min increased plasma osmolality (Osm) 20 mOsm/1 ($N = 10$). TRP decreased an average of 5% ($P < 0.05$). Simultaneously increasing plasma $[K^+]$, $[Mg^{2+}]$, and Osm ($N = 10$) 0.4 mEq/1, 1.95 mEq/1, and 22 mOsm/1 respectively, produced a decrease in TPR of 11% ($P < 0.05$). Identical experiments were carried out in spinally anesthetized (procainized) dogs. Singly increasing plasma $[K^+]$ ($N = 10$), $[Mg^{2+}]$ ($N = 10$) or simultaneously increasing plasma $[K^+]$ and $[Mg^{2+}]$ ($N = 8$), produced significant decreases in TPR. Hypersomolality ($N = 11$) and the combination of hyperkalemia, hypermagnesemia and hyperosmolality ($N = 10$) produced significantly greater decreases in TPR than seen in spinally intact animals. Appropriate control solutions were infused for intact ($N = 18$) and spinally anesthetized ($N = 20$) dog experiments. These data strongly suggest that part of the fall in arterial blood pressure seen in intact dogs during various acutely produced electrolyte and water abnormalities is due, at least in part, to a fall in TPR. They also indicate that ABP responses in intact dogs during various single electrolyte abnormalities may be masked because of operable neurologic barostatic mechanisms.

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1. Emerson, T. E., Jr., Scott, J. B., and Haddy, F. J., Amer. J. Physiol. **218**, 234 (1970).

2. Haddy, F. J., Scott, J. B., Emerson, T. E., Jr., Overbeck, H. W., and Daugherty, R. M., Jr., Circ. Res. **24**, and **25**, I-59 (1969).

3. McKeag, D. B., Emerson, T. E., Jr., and Haddy, F. J., Clin. Res. **17**, 514 (1969).

4. Anderson, D. K., Brace, R. A., Roth, S. A., Radawski, D. P., Scott, J. B., and Haddy, F. J., Circ. Res. **31**, 165 (1972).

5. Chen, W. T., Anderson, D. K., Scott, J. B., and Haddy, F. J., Proc. Soc. Exp. Biol. Med. **140**, 820 (1972).

6. Chou, C. C., and Emerson, T. E., Jr., Amer. J. Physiol. **215**, 1102 (1968).

7. Emerson, T. E., Jr., Parker, J. L., and Jelks, G. W., Clin. Res. **19**, 642 (1971).

8. Haddy, F. J., and Scott, J. B., Physiol. Rev. **48**, 688 (1968).

9. Scott, J. B., Daugherty, R. M., Jr., Overbeck, H. W., and Haddy, F. J., Fed. Proc. **27**, 1403 (1968).

10. Mellander, S., Johannsson, B., Gray, S., Jonsson, O., Lundvall, J., and Ljung, B., Angiologica **4**, 310 (1967).

11. Koch-Weser, J., Amer. J. Physiol. **204**, 957 (1963).

12. Krovetz, L. J., Mitchell, B. M., and Newmaster, T., Amer. Heart J. **74**, 453 (1967).

13. Logic, J. R., Krotkiewski, A., Koppius, A., and Surawicz, B., Amer. J. Physiol. **215**, 14 (1968).

14. Maxwell, R. J., Elliot, R. B., and Robertson, E. S., Amer. J. Cardiol. **13**, 798 (1964).

15. Scott, J. B., Frohlich, E. D., Hardin, R. A., and Haddy F. L., Amer. J. Physiol. **201**, 1095 (1961).

16. Uchiyama, O., Japan. Circ. J. **32**, 359 (1968).

17. Emerson, T. E., Jr., Amer. J. Physiol. **210**, 933 (1966).

18. Gazitua, S., Scott, J. B., Chou, C. C., and Haddy, F. J., Amer. J. Physiol. **217**, 1216 (1969).

19. Gazitua, S., Scott, J. B., Swindall, B., and Haddy, F. J., Amer. J. Physiol. **220**, 384 (1971).

20. Rand, P. W., and Lacombe, E., Radiology **85**, 1022 (1965).

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