gelatin did not cause lipemia, though it readily saturated the reticular endothelial system. The mechanism by which the shellac induces lipemia is obviously different from that of protamine. India Ink does not prevent *release* of clearing factor (lipoprotein lipase). Heparin injected at peak of the India Ink-induced lipemia reduces the lactescence much more than it reduces total fatty acid level.

We wish to thank Dr. J. Campbell for his advice concerning determination of blood lipids.

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Received January 29, 1960. P.S.E.B.M., 1960, v103.

Effects of L-Norepinephrine on Cardiac Metabolism of Dogs in Hemorrhagic Shock.* (25668)

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Earlier studies in this laboratory have demonstrated a biochemical abnormality of the hearts of dogs in hemorrhagic shock, manifested mainly by a negative extraction of pyruvate by the myocardium. It was also shown that a high per cent of these dogs developed subendocardial hemorrhage and necrosis(1). Since it was hypothesized that these deleterious changes might be partly related to increased secretion of epinephrine during shock, it was felt that detailed studies of the effects of sympathomimetic substances in shock were indicated. We have previously shown that l-norepinephrine does not increase survival rate when given to dogs 10 minutes or longer after production of hemorrhagic hypotension (2), and we have further shown that incidence of myocardial lesions is greater in animals so treated(3). The present report is an extension of the earlier reports, and will be concerned with the effects of l-norepinephrine treatment on some aspects of the myocardial metabolism of dogs in hemorrhagic shock.

Methods. The methods briefly described here have been previously described in detail (1,2). Eighteen mongrel dogs were premedicated with subcutaneous morphine sulfate (3 mg/kg body weight) and anesthetized with equal parts of Dial-urethane† and sodium pentobarbital (0.25 ml of this mixture/kg body weight) given intravenously. Each dog was given 200,000 units of penicillin and 0.2 g of streptomycin intramuscularly, and 5 mg/kg of heparin intravenously before the experiment. The aorta, pulmonary artery and coronary sinus were catheterized *via* the femoral artery and jugular veins, respectively, under fluoroscopic control. Systemic arterial and coronary sinus blood samples were analyzed for O_2 and CO_2 (Van Slyke manometric technic), pyruvate(4), lactate(5) and glucose(6). Samples were drawn during the initial control period following which the dogs were bled from the femoral artery over a 10 minute pe-

* This work was supported by grants from U. S. Public Health Service and Cleveland Area Heart Soc.

† The Dial-urethane was generously supplied by CIBA Pharmaceutical Products, Inc., Summit, N. J.

TABLE I. Effects of L-norepinephrine (Series A) or of Blood Infusion (Series B) on Myocardial Metabolism during Shock. (Mean values ± standard error.)

		a. Control	b. Shock	c. Nor-epin. (Series A)	d. Blood (Series B)	Statistical evaluation a–b	b–c	b–d
Pyruv.	Art.	1.43 ± .14	2.47 ± .19	2.48 ± .35	3.95 ± .41	*	0	*
	A–V	.67 ± .11	−.24 ± .15	.18 ± .20	1.01 ± .26	*	0	*
	A–V/A	41.4 ± 6.6	−7.9 ± 6.2	3.2 ± 8.5	27.3 ± 6.2	*	0	*
Lact.	Art.	12.8 ± 1.2	77.9 ± 4.7	77.6 ± 5.9	65.0 ±12.1	*	0	0
	A–V	6.2 ± .9	5.6 ± 2.1	2.2 ± 2.0	14.0 ± 2.9	0	0	†
	A–V/A	46.5 ± 4.5	9.1 ± 3.0	3.7 ± 3.2	26.2 ± 7.1	*	0	†
Glue.	Art.	107.0 ± 6.5	306.9 ±46.4	154.5 ±49.9	222.0 ±36.6	*	†	0
	A–V	5.4 ± .6	−3.3 ± 6.5	−.2 ± 8.7	−3.5 ± 2.1	0	0	0
	A–V/A	7.2 ± 1.8	4.6 ± 4.0	7.2 ± 3.9	−2.2 ± 1.5	0	0	0
O_2	Art.	18.1 ± .6	13.6 ± .7	12.2 ± 1.0	18.2 ± 1.1	*	0	*
	C.S.	4.9 ± .5	1.6 ± .3	5.1 ± .9	5.9 ± .8	*	*	*
	A–V/A	73.6 ± 2.2	89.2 ± 1.5	56.0 ± 7.9	67.2 ± 4.3	*	*	*
	Sat'n	91.5 ± 1.2	86.1 ± 2.7	86.2 ± 3.3	93.0 ± 2.3	0	0	0

Statistical evaluation: * Significant difference, with probability <.01 that observed differences could be due to chance. † Significant difference, with probability <.05 and >.01. 0 = No statistically significant difference.

Abbreviations: Art. = Arterial level in mg (or vol) %. A–V = Coronary arteriovenous difference (mg %). A–V/A = Percent extraction (%). C.S. = Coronary sinus level (vol %). Sat'n = Oxygen saturation (%).

riod into a reservoir set to maintain mean systemic blood pressure at 30 mm Hg. After 45 minutes of sustained hypotension, blood samples were again drawn. In one series of 12 dogs (Series A) the cannula between aorta and reservoir was then clamped and an intravenous infusion of l-norepinephrine bitartrate (24 μg/ml) was given at a rate that increased mean arterial blood pressure to 80-90 mm Hg within 5 minutes. Rate of the drip was set to maintain this level of pressure. After 15 minutes the 3rd set of determinations was made, with reservoir blood being reinfused at the same rate that it was withdrawn in the sampling procedure. A second series of 6 dogs (Series B) was studied in this same manner except that, instead of l-norepinephrine, the reservoir blood was infused at a rate that maintained arterial blood pressure at 80-90 mm Hg.

Results. Confirming previous studies from this(1) and other(7) laboratories, a negative myocardial extraction of pyruvate is found during hemorrhagic shock in dogs (Table I). Although extraction (A-V) of lactate is maintained in shock, it is in the face of a markedly increased arterial level, so that the per cent extraction (A-V/A) of lactate during shock is significantly decreased. Infusion of l-norepinephrine does not cause significant change in this picture, but reinfusion of whole blood causes immediate reversion of both pyruvate and lactate extractions toward normal. There is great variation in glucose findings during shock and after treatment with blood or norepinephrine, so that the main change of significance is the increased arterial level of glucose during shock.

These metabolic observations may help to explain our previous finding that l-norepinephrine treatment does not increase per cent survival of dogs in shock(2) and, in fact, results in increased incidence and severity of myocardial damage(3). When hemorrhagic shock is treated by l-norepinephrine without relieving the oligemia, cardiac output is not changed and vascular resistance in the extremities (as determined by paw blood flow) is further increased(2). Since the basic metabolic abnormality is not relieved, the heart is less able to handle the increased work load imposed on it. On the other hand, when blood pressure is increased by blood infusion, cardiac output is returned to the normal range and vascular resistance of the extremities is decreased. Under these circumstances the metabolic pattern of the myocardium reverts to normal.

The reason for the abnormal metabolism of the heart during shock is not known, but it is

possible that a toxic product of the peripheral ischemia, transported to the heart, may cause a block in myocardial enzyme systems. Such a "circulating lethal toxin" has been reported by Schweinburg, *et al.*(8).

The observation that l-norepinephrine does not increase incidence of survival in these circumstances has been confirmed by others(9, 10). However, when pressor therapy is instituted very early in the experiment, survival rate appears to be increased(11,12). It is known that cardiovascular responsiveness varies during different stages of shock, so that cardiac output will increase with l-norepinephrine early in shock, but not during later stages(13). Caliva, *et al.*, using polarographic technics, have suggested that the very early treatment of hemorrhagic shock, "because it results in the restoration of oxygen levels, might well prevent or correct metabolic abnormalities"(14).

These findings are compatible with the concept that hypotension by itself, in the absence of excess sympathomimetic activity, is not necessarily deleterious to the myocardium. We have previously shown that marked hypotension produced in human subjects by high spinal anesthesia does not result in evidence of myocardial anoxia or in myocardial metabolic derangements(15). Similarly, Remington, *et al.*, have demonstrated that dibenamine increases survival rate of dogs in hemorrhagic shock(16). Although the bleeding volume is less in the dibenamine-treated dogs, it is apparent that the hypotension alone is not the primary lethal factor. The authors suggest that vasoconstriction, which is presumably prevented by the adrenergic blocking agent, is a precipitating factor in irreversibility.

Summary and conclusions. The myocardial metabolism of 18 intact dogs was studied during an initial control period and after production of hemorrhagic shock. Some of the dogs were subsequently treated with l-norepinephrine and some with blood. An abnormal myocardial metabolic pattern was demonstrated during shock which was relieved by blood infusion but not by l-norepinephrine. It is suggested that the reason that l-norepinephrine treatment does not increase survival rate of dogs in shock is because it does not correct the basic metabolic abnormality and at the same time imposes a heavier burden of work on the heart.

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Received February 1, 1960. P.S.E.B.M., 1960, v103.