responds to enzymatically changed transferrin, which has preserved the antigenic properties involved in the immuno-electrophoretic procedure(12,13,14).

Chevance, Galli, Jeanmaire, and Gerard(6) have recently described an immuno-electrophoresis with specific CSF antiserum. They have described 9 precipitation lines, among them a slowly moving gamma globulin. However, as mentioned by Burtin, the explanation of the immuno-electrophoretic findings was limited by lack of a potent antiserum. The data given here support the findings by Chevance *et al.*(6) of a slowly moving fraction in CSF with a mobility slower than that of the serum gamma globulin, antigenically different from serum gamma globulin. Both the absorption experiments with normal human serum and the crossing of the 2 slowest moving precipitation lines seem to exclude a very close antigenic relation between serum gamma globulin and gamma-CSF (Fig. 1). These findings may account for some of the slowest moving gamma globulin fractions revealed in agar gel micro-electrophoresis and explain the selective increase of these in diseases of the central nervous system (Fig. 1).

Summary. Immuno-electrophoresis of normal concentrated cerebrospinal fluid, developed with a specific rabbit anti cerebrospinal fluid antiserum, has demonstrated the existence in the gamma and beta areas of 2 proteins not found in serum.

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Received March 7, 1961. P.S.E.B.M., 1961, v107.

A Study of the Mechanism of the Increase in Cardiac Output Induced by Isopropylarterenol Hydrochloride (Isuprel®).* (26570)

JIRO NAKANO, JOHN C. MCGIFF†, HORST ZEKERT,‡ CHARLES B. JENNEY§, H. N. WELLMAN‖, AND RENÉ WÉGRIA

Department of Medicine, Saint Louis University School of Medicine and the University Hospital (Firmin Desloge Hospital), Saint Louis, Mo.

Many investigators(1-5) have studied the effect of isopropylarterenol hydrochloride (Isuprel®) on various aspects of the circulation and have demonstrated that the drug increases heart rate and cardiac output, decreases mean arterial blood pressure or leaves it unchanged, and lowers total peripheral resistance. To evaluate the role of the rise in heart rate normally induced by Isuprel in the genesis of the increase in cardiac output caused by the drug, the effect of Isuprel on

* This work was made possible by a grant-in-aid from the Harry Freund Memorial Foundation.

† Fellow of Am. Heart Assn.

‡ Postdoctorate Fellow, U. S. Public Health Service.

§ Student Fellow, U. S. Public Health Service.

‖ Student Fellow, Nat. Science Foundation.

cardiac output and arterial blood pressure of the whole animal was investigated while heart rate was kept constant during the period of action of the drug.

Methods. Ten dogs (18.2-37.7 kg) were anesthetized by intravenous administration of 100 mg of chloralose per kg. The methods used to measure and record continuously the output of the left ventricle (CO), and the mean arterial blood pressure (MABP), as well as the formula used to calculate total peripheral resistance (TPR) have been described(5-10). The heart rate (HR) was obtained from electrocardiographic tracings. Atrial (4 experiments on 2 dogs) or ventricular (13 experiments on 8 dogs) tachycardia of the desired rate was induced electrically with a Grass stimulator, short DC stimuli of minimal intensity being applied to the left atrium or the left ventricle through 2 fishhook electrodes. In a first series of 8 experiments on 5 dogs (Part A, Fig. 1), after a control period, tachycardia was induced, then after 65 to 184 seconds of tachycardia a 0.0005% Isuprel solution in 0.9% NaCl solution was administered intravenously at the average rate of 4.6 ml/min, while tachycardia was maintained. Administration of the drug lasted from 100 to 176 seconds. Amount of the drug administered ranged between 0.9 and 3.6 μg/kg. Administration of the drug was then discontinued and tachycardia maintained for another 123 to 240 seconds, after which it was discontinued and a period of recovery allowed. This sequence of observations was repeated in 3 of the 5 dogs. In another series of 9 experiments on 5 dogs (Part B, Fig. 1), the effect of comparable doses of Isuprel, administered as a 0.001% solution, on CO and MABP was first studied, then, after a period of recovery, the effect of a similar dose of the drug during ventricular tachycardia was investigated as described in the first series of experiments. This sequence of studies was also repeated in 4 of the 5 dogs. The amounts of 0.9% NaCl solution administered as vehicle for the drug have been shown previously to have no effect on the parameters studied(8).

Results. The results were strikingly constant. They are summarized in Fig. 1. In a representative experiment, illustrated by the broken lines of Fig. 1, Part B, 1.4 μg of Isuprel per kg administered over a 111 second period raised the HR from 156 to 216/min and increased CO and stroke volume (SV) from 1920 ml and 12.3 ml to 2700 ml and 12.5 ml respectively. The MABP remained essentially unchanged and TPR decreased from 83 to 60 arbitrary units. After Isuprel was discontinued, all parameters returned to or toward control values. Induction of ventricular tachycardia of a rate of 240/min resulted in a marked, sudden and immediate drop in CO and MABP, as previously reported(11). CO and MABP then returned to or toward control, and by the end of 90 seconds of tachycardia, MABP, CO, SV and TPR stabilized around values of 128 mm Hg, 1250 ml, 5.2 ml and 102 units respectively. The ventricular tachycardia being maintained, a dose of Isuprel of 1.4 μg/kg administered over a 140 second period, *i.e.*, a dose of the drug similar to the dose injected a few minutes previously, resulted in an increase in CO and a decrease in TPR similar in magnitude to the changes of CO and TPR observed during injection of a similar dose of the drug while the dog had a spontaneous sinus rhythm. However administration of Isuprel during the tachycardia definitely raised the MABP instead of lowering it or leaving it unchanged, as observed when similar doses of the drug are administered during spontaneous sinus rhythm in the present and previous experiments(5). Upon cessation of the drug administration and while ventricular tachycardia was maintained, all parameters returned to or toward the value they had during the tachycardia before injection of Isuprel. Upon cessation of ventricular tachycardia, all parameters returned to or toward their control. Similar effects were obtained when, after a period of recovery, a similar dose of Isuprel was administered again first during spontaneous sinus rhythm, then during ventricular tachycardia.

Discussion. The mechanisms of the hemodynamic effect of Isuprel alone and induced tachycardia alone have been discussed(5,11).

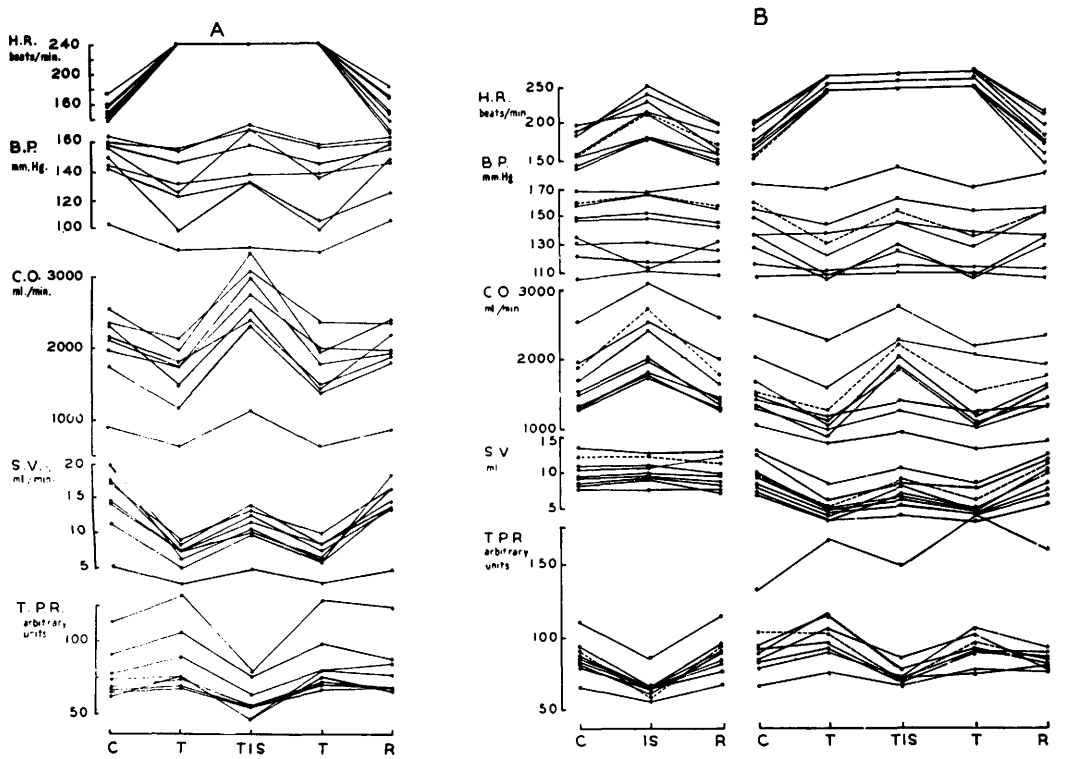

FIG. 1. Effect of isopropylarterenol hydrochloride (Isuprel®) on heart rate (HR), mean arterial blood pressure (BP), cardiac output (CO), stroke volume (SV) and total peripheral resistance (TPR). Part A pictures experiments of the first type described in text; Part B, experiments of second type, in which Isuprel was injected first during spontaneous cardiac rhythm then during tachycardia. C, control period; T, electrically induced tachycardia; TIS, electrically induced tachycardia and administration of Isuprel; R, recovery period; IS, period of Isuprel administration. Values of HR, MABP, CO, SV and TPR during period of Isuprel administration are values obtained when continuous administration of Isuprel had resulted in a progressive rise of CO to a maximal and stable level. Values of HR, MABP, CO, SV and TPR during tachycardia are values obtained when MABP and CO had become stabilized. Values of HR, MABP, CO, SV and TPR during tachycardia and Isuprel administration are values obtained when CO and MABP had become stabilized.

When Isuprel is administered during induced tachycardia, the results are essentially similar to those observed in normal anesthetized dogs with spontaneous sinus rhythm, in which HR is raised by the drug. SV and CO rise, but since HR does not change after administration of Isuprel during tachycardia, this increase in CO is due exclusively to the increase in SV. This increase in SV is presumably due to the same mechanisms as those operating while the drug is also allowed to modify HR, *i.e.*, its direct inotropic effect on the myocardium(1-5,12) and its vasodilatation effect(1-5). The intensity of the effect of the drug on CO during tachycardia seems to be similar to that of its effect when administered to the anesthetized animal with spontaneous sinus rhythm and it would seem logical to conclude that preventing the drug from increasing HR does not keep it from increasing CO. Isuprel lowers TPR of the animal during tachycardia although MABP may be observed to rise presumably because of the increase in CO. It is not clear why the increase in CO produced by Isuprel in the anesthetized dog with normal sinus rhythm is accompanied by an unchanged or even lowered MABP whereas a similar increase in CO due to the same dose of Isuprel generally raises MABP in the anesthetized dog with a fixed HR due to electrically induced tachycardia. It must be presumed that the difference is due to the peripheral constriction caused by the reduction in CO occurring during the elec-

trically induced tachycardia. Apparently the vasodilating effect of Isuprel does not offset completely the vasoconstriction due to the reduction of CO produced by the tachycardia, and Isuprel raises MABP when administered during tachycardia. It is possible that this increase in MABP might disappear if administration of Isuprel was continued longer than in the present experiments.

Other drugs such as nitroglycerine increase both HR and CO(13,14), apparently exclusively through their vasodilating property since they are not known to have any direct effect on the myocardium. The present experiments concerning Isuprel do not necessarily permit the conclusion that nitroglycerine, like Isuprel, would increase cardiac output even if it were prevented from increasing HR. Arteriovenous fistula is also known to increase both HR and CO(15) and the increase in HR has been proven experimentally not to be a *sine qua non* for the increase in CO(15).

Summary. The effect of Isuprel on MABP, CO and TPR has been investigated in the anesthetized dog in which the effect of the drug on HR is allowed to occur, as well as in the anesthetized dog in which electrically induced atrial or ventricular tachycardia is initiated before and maintained throughout period of action of the drug to prevent the increase in heart rate normally induced by the drug. Under the circumstances of drug dosage, rate of the induced tachycardia as well as control values of HR and CO, the effect of the drug on CO and TPR is essentially the same, whether the effect of the drug on HR is permitted or prevented.

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Received January 23, 1961. P.S.E.B.M., 1961, v107.

Studies with Mouse Pituitary Thyrotropic Tumors. II. Restored Responsiveness in Semi-Responsive Strain Surgically Reduced in Size.* (26571)

SIDNEY C. WERNER AND RAUL GRINBERG

Department of Medicine, Columbia University College of Physicians and Surgeons

A study has been made of the effect upon responsiveness to thyroxine of surgical reduction in size of an autonomous semi-responsive thyrotropic mouse pituitary tumor which had grown so large as to be no longer suppressible by this hormone. Of the 3 types of strains of thyrotropic mouse pituitary tumor isolated by Furth(1), dependent responsive, autonomous

* Aided by contract from Cancer Chemotherapy Nat. Service Center, Nat. Cancer Inst., U.S.P.H.S.