

## Neutralization of Angiotonin by Normal and by Ischemic Kidney Blood Plasma.

MEYER FRIEDMAN.

*From the Harold Brunn Institute for Cardio-Vascular Research, Mount Zion Hospital, San Francisco, Calif.*

The blood<sup>1</sup> leaving the partially ischemic kidney has been found to differ from normal systemic blood in that it contains a pressor substance similar to angiotonin<sup>2</sup> in its physiological action, but dissimilar in its chemical properties.

In the present communication evidence is presented which indicates that blood leaving the hemodynamically altered kidney also differs from normal blood in its comparative inability to neutralize the pressor action of angiotonin.

*Methods.* In each of 6 experiments a dog was anesthetized with pentobarbital sodium. Sufficient arterial blood was then obtained by femoral puncture for 3 samples (5 cc each) of plasma. The left kidney of each dog was exposed, the left renal artery partially clamped, and 75-100 cc of renal venous blood were collected as described in a previous report.<sup>1</sup> Purified heparin (Connaught) was used as the anti-coagulant. Five samples (5 cc each) of plasma were obtained from this renal blood collection. Thus, from each dog 3 samples of normal blood plasma and 5 samples of ischemic kidney plasma were obtained. Angiotonin (0.2 to 0.8 cc) was added to each of the 3 normal blood plasma samples and to 3 of the 5 renal plasma samples. All samples, including the 2 remaining renal plasma samples, were incubated at 38°C for one hour. In each experiment, angiotonin alone, equal in quantity to the amount added to the plasma samples, was also incubated.

The various samples, after incubation, were injected in the femoral vein of an anesthetized, previously nephrectomized dog (24 hours) and the pressure changes continuously followed by means of a mercury manometer connected by cannula to the femoral artery.

*Results.* As Table I and Fig. 1 indicate, there is practically complete neutralization of the angiotonin by the normal systemic blood plasma after an hour's incubation. The average pressure rise following the injection of the normal blood plasma-angiotonin mixtures was 5 mm of Hg, and only in Experiment VI was there a sig-

<sup>1</sup> Friedman, M., Selzer, A., and Sampson, J., *Am. J. Physiol.*, 1941, **131**, 799.

<sup>2</sup> Page, I. H., and Helmer, O. M., *J. Exp. Med.*, 1940, **71**, 29.

nificant rise following its injection. However, it was found that ischemic kidney plasma lacked the property of angiotonin neutralization possessed by normal systemic blood plasma, for the average rise following the injection of ischemic kidney blood plasma-angiotonin mixture was 20 mm of Hg. This latter rise was comparable to the pressor effect obtained following the injection of angiotonin in saline alone. The pressor rise following the injection of the ischemic kidney plasma-angiotonin mixture was not due to the pressor property of ischemic kidney blood for, as can be seen by an examination of the data, the rise following injection of 5 cc of incubated ischemic kidney blood plasma was negligible.

*Discussion.* It has been recognized<sup>3</sup> that angiotonin and its counterpart, hypertensin,<sup>4</sup> may be inhibited by normal blood plasma.

TABLE I.  
Effect of Ischemic Kidney Blood Plasma and Normal Blood Plasma on Angiotonin.

| Exp. No. | Amt of angiotonin (cc) | Blood pressure effect of angiotonin alone (mm of Hg) | Blood pressure effect of angiotonin plus ischemic kidney plasma* (mm of Hg) | Blood pressure effect of angiotonin plus normal plasma† (mm of Hg) | Blood pressure rise of ischemic kidney plasma alone‡ (mm of Hg) |
|----------|------------------------|------------------------------------------------------|-----------------------------------------------------------------------------|--------------------------------------------------------------------|-----------------------------------------------------------------|
| I-a      | 0.2                    | +30                                                  | +15                                                                         | 0                                                                  | +8                                                              |
| -b       | 0.2                    |                                                      | +20                                                                         | 0                                                                  | +4                                                              |
| -c       | 0.2                    |                                                      | +20                                                                         | 0                                                                  |                                                                 |
| II-a     | 0.2                    | +20                                                  | +20                                                                         | 0                                                                  | +3                                                              |
| -b       | 0.2                    |                                                      | +15                                                                         | 0                                                                  | +5                                                              |
| -c       | 0.2                    |                                                      | +15                                                                         | + 5                                                                |                                                                 |
| III-a    | 0.3                    | +23                                                  | +20                                                                         | + 3                                                                | +2                                                              |
| -b       | 0.3                    |                                                      | +15                                                                         | +12                                                                | +3                                                              |
| -c       | 0.3                    |                                                      | +18                                                                         |                                                                    |                                                                 |
| IV-a     | 0.5                    | +27                                                  | +20                                                                         | 0                                                                  | +5                                                              |
| -b       | 0.5                    |                                                      | +19                                                                         | + 2                                                                | +6                                                              |
| -c       | 0.5                    |                                                      |                                                                             | + 2                                                                |                                                                 |
| V-a      | 0.5                    | +20                                                  | +17                                                                         | +10                                                                | +2                                                              |
| -b       | 0.5                    |                                                      | +13                                                                         | + 5                                                                | 0                                                               |
| -c       | 0.5                    |                                                      | +17                                                                         |                                                                    |                                                                 |
| VI-a     | 0.8                    | +35                                                  | +32                                                                         | +15                                                                | +4                                                              |
| -b       | 0.8                    |                                                      | +32                                                                         | +15                                                                | 0                                                               |
| -c       | 0.8                    |                                                      | +32                                                                         | +12                                                                |                                                                 |
| Avg      | .41                    | +26.0                                                | +20.0                                                                       | + 5.0                                                              | +3.5                                                            |

\*Five cc of ischemic kidney plasma were used in each experiment.

†Five cc of normal plasma were used in each experiment.

‡Five cc of incubated ischemic kidney plasma injected in each experiment.

<sup>3</sup> Page, I. H., and Helmer, O. M., *J. Exp. Med.*, 1940, **71**, 495.

<sup>4</sup> Munoz, J. M., Braun-Menendez, E., Fasciolo, J. C., and Leloir, L. F., *Am. J. M. Sc.*, 1940, **200**, 608.

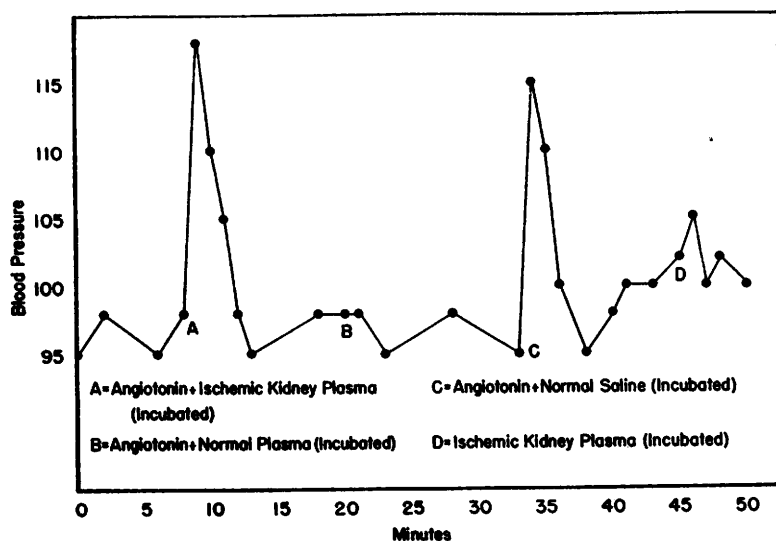


FIG. 1.

*Experiment II-A*—The pressor effect of 5 cc of ischemic kidney blood plasma, 5 cc of normal blood plasma incubated with 0.2 cc of angiotonin solution, and 5 cc of incubated kidney blood plasma.

Although there is strong evidence<sup>1</sup> that purified angiotonin is not exactly similar to the pressor substance found in blood leaving the partially ischemic kidney, it is possible that, because of the extensive chemical procedures necessary for the isolation of angiotonin, certain chemical changes might have occurred in the original substance. If, however, angiotonin does represent the essential chemical derivative of the original effector substance leaving the kidney when its hemodynamics have been seriously altered, then the inability of the venous blood plasma leaving this same kidney to neutralize angiotonin indicates that there may be two mechanisms involved in this type of renal derangement. The evidence presented here suggests strongly that one of these mechanisms is a decreased ability of the blood leaving such an abnormal kidney to neutralize angiotonin.

*Conclusion.* (1) The ability of normal systemic blood plasma to neutralize angiotonin is markedly decreased after circulation through the partially ischemic kidney.

The angiotonin used in these experiments was graciously supplied to us by Dr. Irvine H. Page.