Effect of Liver Damage on Experimental Renal Hypertension in the Rat

By H. F. Loyke, M.D., J. J. Plucinsky, M.D., and T. L. Crawford, M.D.

Patients who have had prolonged established arterial hypertension, and who later develop cirrhosis of the liver, show persistent associated decrease of blood pressure. This suggests that intact hepatic function is one of the factors that maintain arterial pressure and agrees with observations of others. The onset of acute infectious hepatitis in patients with pre-existing hypertension is accompanied by a drop in blood pressure which returns to its former levels after jaundice subsides. Raaschou found that prevalence and degree of hypertension are diminished during fatal subacute hepatic atrophy, as compared with patients dying of other causes.

This association has been experimentally confirmed. Davis and Tanturi noted a reduction in blood pressure in renally hypertensive dogs subjected to subtotal hepatic arterial occlusion. Kaaschou and Trautner, after establishing renal hypertension in 6 dogs, induced liver damage by obstructing the common bile duct and found a gradual reduction of the blood pressure in each.

The present report describes effects of graded and reversible liver damage in rats with renal hypertension.

Methods

Orienting Experiments

These had shown: (a) that uninephrectomy with contralateral perirenal figure of eight ligature resulted in sustained hypertension; (b) that semi-weekly injections of 0.3 mg./Kg. of CCl₄ (administered subcutaneously in all instances) provoked hepatic injury, ranging from fatty metamorphosis to cirrhosis depending on the number of injections (ranging up to 31 in this group of 5 rats), but did not elicit hypertension or provoke histologically renal injury.

Present Experiments

Observations were made in 6 control and 26 experimental female albino rats of about 150 Gm. body weight, maintained on Purina rat chow. Of the 26 animals in the experimental group (fig. 1), 4 failed to develop hypertension (systolic pressure greater than 160 mm. Hg, Friedman microphonic method) until 1 per cent NaCl was substituted for drinking water. Pressure and weight measurements were made twice weekly. Subcutaneous injections of CCl₄ were given after 2 weeks of persistent hypertension. The 22 rats with renal hypertension were given initial doses of 0.3 ml./Kg., repeated 1 to 5 times; subsequent doses were reduced to 0.15 ml./Kg., which dosage was given to renal-saline group. Kidneys and livers of experimental and control animals were examined microscopically at the end of the experiment. Serum total protein and albumin concentrations were measured during control and test periods.

Results

Of the 26 test animals, all developed pressures greater than 180 mm. Hg; 5 (nos. 11, 12, 21, 23, 26 and 27) died shortly after the initial larger doses of CCl₄. The remainder demonstrated pressure reductions of more than 50 mm. Hg (average drop 74). Moderate increase of pressures were recorded in the normal controls, all of which gained weight (final average 262 Gm.).

Weight loss averaged 16 Gm. in 14 test animals that had received the larger doses. On smaller doses, this weight was maintained, 4 did not lose weight and 3 gained an average of 8 Gm. Of the renal-saline group, weight was unchanged in 3, and 1 gained 8 Gm. (final average weight, 205 Gm.).

Serum albumin and globulin concentrations were initially normal; however, the albumin fell in 16 and rose in 9 of the hypertensive group, while the globulin rose in 20 and fell in only 2, 3 remaining unchanged. With liver
Control.

Figure 1

Highest systolic blood pressure (*) detected by Friedman method. Arrow (v) shows the lowest pressure dropped to following liver damage with CCl₄.

Figure 2

Effect of liver disease on hypertension.

damage the albumin fell in 16 of 17, globulin fell in 10, rose in 5, and remained unchanged in 2 animals.

Three animals (nos. 13, 22 and 25) survived CCl₄ treatment and after its discontinuance the systolic pressure returned to its previous hypertensive levels. Reinstitution of CCl₄ injections in 2 animals (nos. 13 and 22) which survived 4 weeks again decreased blood pressure to normotension. The course of 1 of these is shown in figure 2 and its hepatic morphology in figure 3A.

Discussion

The data demonstrated that CCl₄ intoxication consistently decreases blood pressures of renally hypertensive rats to normotensive levels and this effect was sequentially demonstrated in 2 of the test animals. The effect cannot be attributed to renal tubular injury; further, with the doses used, it showed no association with weight loss or inanition. It was consistently associated with hepatic injury which might be mild (fig. 3A) or severe (fig. 3B) and, in the surviving animals, reversible. The data is in accord with the finding that clinical hypertension may be remitted by any degree of hepatic injury that is more than minimal.

In renally hypertensive dogs subjected to bile duct obstruction and in hypertensive patients developing cirrhosis, decreased blood pressure shows an association with decreases in albumin/globulin ratio. Demonstration of this in rats is complicated by the effects of

Figure 3A

Animal 22, showing a moderate degree of fatty metamorphosis of the liver. Blood pressure at this time was 160 mm. (X 125.)

Figure 3B

Animal 14, showing fatty metamorphosis with fibrosis of the liver and pressure of 160 mm. (X 125.)
renal hypertension on these serum fractions. Four rats (nos. 4, 10, 22 and 32) had reversal of A/G ratio, and 7 rats (nos. 1, 2, 14, 15, 24, 25 and 29) had ratios of 1-to-1 during CCl₄ treatment.

The mechanism of the antihypertensive effect of hepatic injury is unexplained. Decreases in serum content of angiotensinogen (renin substrate, an α₂-globulin of hepatic origin) have been found experimentally under conditions of severe or total liver insufficiency and clinically in patients with liver disease. However, methods used in the reported assays on patients have been considered no more than semiquantitative. Hence, until more satisfactory procedures are applied under experimental conditions, such as those described above, and in patients with liver disease, the present data reaffirm the role of the liver in the maintenance of hypertension but do not establish the mechanism of action.

Summary

Renal hypertension was produced in 26 test rats and fell to normal levels when they received CCl₄. Our data indicate that this is due to liver damage and not to general inanition. These changes are reversible, since cessation of CCl₄ injections led to blood pressure rise. Morphologically, only a moderate degree of fatty metamorphosis is necessary to cause the blood pressure to fall from hypertensive levels to normotension. The biochemical change involved variable changes in albumin and globulin.

Acknowledgment

We are grateful to Dr. John MacKrell, Pathologist at St. Vincent Charity Hospital, for his interpretations of histologic slides.

Summario in Interlingua

Hypertension renal esseva inducita in 26 rattos de experimentation. Le hypertension descendeva a nivegli norma quando le rattos recipera injectiones de CCl₄. Nostre datos indican che iste effetto esseva causata per dannos hepatic e non per inanition general. Le dannos in question es reversibile, proque le cessation del injectiones de CCl₄ resultava in un augmento del tension de sanguine. Morphologicamente, un grado moderate de metamorphosis grassa suffice pro causar un reduction del hypertension a un nivello normotensive. Le alterationes biochimic inbedulava variabile alterationes de albumina e de globulina.

References

Effect of Liver Damage on Experimental Renal Hypertension in the Rat
H. F. LOYKE, J. J. PLUCINSKY and T. L. CRAWFORD

Circ Res. 1960;8:535-537
doi: 10.1161/01.RES.8.3.535

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1960 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/8/3/535

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/