Antihypertensive Effect of Transplant of Rat Kidney or Its Unclipping
Hemodynamic Effects and Control Mechanisms

SIBLEY W. HOOBLER, M.D., TANENAO ETO, M.D., RICHARD WELK, B.S.,
AND HARRIET BURGE, PH.D.

SUMMARY The acute transplantation of a normal kidney into a recipient rat with Goldblatt one-kidney, one clip hypertension (1K1C) results in a blood pressure (BP) fall toward but not below normal levels within 1 hour. Removal of the clip in a 1K1C hypertensive rat also normalizes the BP rapidly. These changes are not mediated by external fluid loss and occur after indomethacin pretreatment, but are associated with a fall in cardiac output. The mechanism of release of a depressor secretion from the kidney transplant appears to be under barostatlc control. Thus, transplanting a kidney into a hypertensive recipient caused a prompt BP decline, whereas transplanting an SHR kidney into a hypertensive recipient did not lower the BP. The prompt BP fall seen after unclipping also indicates that abrupt exposure of the kidney to a high perfusion pressure initiates the release of some depressor agent. When the recipient rat was made hypertensive by injecting renin, the kidney transplant did not lower the BP. When angiotensin in subpressor dose was infused into the renal artery of the kidney transplant, the BP of the recipient did not fall, whereas infusion of norepinephrine in equiconstrictor doses did not prevent the depressor response. These experiments suggest that, in addition to a barostatic stimulus for depressor release, angiotensin acts as a specific inhibitor.

(Hypertension 3 (suppl II): II-200-II-204, 1981)

KEY WORDS • experimental renal hypertension • cardiac output • spontaneously hypertensive rat • angiotensin • kidney unclipping

Methods

Transplant Experiment

Rats (200–300 g of body weight), used as recipients, were of four types: 1) SHR aged 12 to 15 weeks; 2) 1K1C hypertensive Sprague Dawley (SD) rats, with BP in excess of 180 mm Hg, 3 to 4 weeks after nephrectomy and 4 to 5 weeks after left renal artery clipping; 3) renoprival rats with acute renin infusion hypertension, and binephrectomized rats receiving 18 hours later 1.0 Goldblatt unit of renin intraperitoneally (i.p.) followed in 5 min by 0.5 units intravenously (i.v.); 4) normotensive SD and Wistar (WI) rats. Donor kidneys were taken from either normotensive SD or WI rats, or SHR (12–15 weeks) with BP in the range of 180–200 mm Hg.

Preparation of donor of the kidney transplant resembled the procedures described by Omae et al.8 In the donor rat, a PE 90 cannula (internal diameter, I.D. = 0.86 mm) was passed up the aorta to the orifice of the left renal artery while a PE 190 (I.D. 1.119 mm) cannula was inserted into the vena cava to a point just below the left renal vein. Both cannulas were clamped

From the University of Michigan, Hypertension Section, Department of Medicine, Ann Arbor, Michigan, and the Cleveland Clinic Foundation, Research Division, Cleveland, Ohio.

Address for reprints: Dr. Sibley W Hoobler, Cleveland Clinic Foundation, Research Division, 9500 Euclid Avenue, Cleveland, Ohio 44106.
after filling with saline solution containing heparin 100 
µ/ml. Attention was then directed to the tracheot-
omized recipient anesthetized with 40–50 mg/kg pent-
tobarbital sodium and 0.15 mg atropine intra-
peritoneally. The femoral artery and vein of this rat 
were cannulated with PE 50 and 90 cannulas respect-
ively. After ligating the ureter of the donor’s kidney 
and injecting 500 units of heparin into the donor and 
250 units into the recipient, the donor’s tubing was 
connected to recipient’s. Donor’s aorta above the left 
renal artery and vena cava below the left renal vein 
were ligated and the clamps released. In this way it 
was possible to establish immediate perfusion of the 
donor kidney by the recipient’s blood. Anesthesia was 
maintained by giving 10 mg/kg pentobarbital sub-
cutaneously every 15 min into the recipient.

For infusion directly into the donor kidney, a T-
tube was inserted at the arterial connection, and 
the side arm pump-perfused with the desired solution at 
a rate of 0.02 ml/min. For renal blood flow measure-
ments a similar T-tube was introduced into the venous 
side. This possessed a long side arm so that the rate of 
inflow of venous blood into it after distal clamping 
could be measured with a stop-watch. After releasing 
the clamp, blood was injected back into the circula-
tion.

Unclipping Experiments

Rats weighing 150 g were operated on to create 
1K1C animals with post nephrectomy hypertension of 4 weeks’ duration. On the day of unclipping, under 
halothane anesthesia, PE 50 cannulas were implanted into the carotid artery and jugular vein. Thirty 
minutes after withdrawal of anesthesia, two baseline 
cardiac output determinations were made 1 hour apart. The rats were then reanesthetized and clips 
were removed or a sham removal performed. Cardiac output determinations were repeated at 60 and 120 
minutes, beginning 30 minutes after the anesthetic 
withdrawal. Cardiac output was measured by inject-
ing 1 mg of cardiogreen dye using a specially prepared 
 injection device. Blood was simultaneously withdrawn from the carotid artery, passed through a specially 
designed cuvette, and returned to the rat after each 
measurement. Cardiac output was calculated from 
dye dilution curves in the usual manner; BP was deter-
mined continuously from the carotid cannula by a 
strain gauge.

Results

Transplant Experiments

Response of Blood Pressure of Chronic Hypertensive
Recipients to Kidney Transplantation

Figure 1 left shows that only a kidney from a normo-
tensive rat will lower the BP of a 1K1C hyperten-
sive recipient. Figure 1 right indicates that the BP of 
an SHR rat undergoes a major reduction only when 
connected to the kidney from a normotensive donor. 
Kidney from donors with hypertension equal to that in 
the recipient did not lower the BP; similarly normo-
tensive-normotensive connections did not change the recipient’s BP.

Renal blood flow (RBF) was determined in six ex-
periments, each where a donor kidney had been con-
ected for 45–50 minutes to various recipients. The 
mean RBF was as follows: normal recipient + normal 
donor 2.5 ± 0.4; SHR + WI 3.0 ± 0.2; SHR-SHR 
2.9 ± 0.2; 1K1C + normal donor 3.0 ± 0.2; 1K1C + 
SHR 3.0 ± 0.2 ml/min. It is apparent that variations 
in RBF were not related to the antihypertensive effects 
of the procedure.

Response to Kidney Transplant of Blood Pressure of
Recipients Acutely Hypertensive from Renin
Injection

Sustained hypertension (150–160 mm Hg) was 
created by injecting hog renin into 12 uni- or bineph-
rectomized recipients. The course of the BP was un-
changed in the six rats in which the transplant was 
opened to the recipient’s circulation.

Intrarenal Administration of Angiotensin II (All) and
Norepinephrine (NE)

The BP change of the SHR at 15 minutes after the 
transplant of a WI kidney receiving an intrarenal All 
infusion (5 ng/kg/min), a NE infusion (10 ng/kg/ 
min), or a saline infusion (0.02 ml/min) was -4 ± 0.8, 
-19 ± 1.9 or -21 ± 2.7 mm Hg, respectively (figure 
2). The BP fall in the All group was significantly less 
than in the other two groups (p < 0.001) vs each 
group. The RBF at 15 minutes after the transplant 
was 3.2 ± 0.2 ml/min for the All group, 3.3 ± 0.2 for 
the NE group, and 3.7 ± 0.2 for the saline group. Infu-
sions of these doses for 15 minutes into the WI 
kidney connected to a WI recipient did not change the 
latter’s BP. The reduction in RBF in the All group 
was not significantly different from that in the NE 
group, but was significantly reduced when compared to 
that in the saline group (p < 0.05). Thus, despite an 
equal reduction in RBF, the depressor effect of the 
kidney transplantation was inhibited by All and not 
by NE.

Changes in Vascular Reactivity of the Recipient

Average of mean BP of the six recipient SHR just 
before the All injection was 184 ± 2 mm Hg. The 
pressor response to a bolus dose of 50 ng/kg of All 
given i.v. was 16 ± 1 mm Hg. When the average mean 
BP of the recipient had fallen to 165 ± 4 mm Hg 
45–60 minutes after the transplant, the pressor 
response to the same dose of All was 16 ± 1 mm Hg. 
Likewise NE responsiveness was unaffected: 0.25 
µg/kg caused a BP rise of 18 ± 1 mm Hg before 
transplant (BP 182 ± 2 mm Hg) and 20 ± 2 mm Hg 
afterward when the BP had fallen to 163 ± 3 mm Hg.

Indomethacin Blockade

Six SHR recipients and WI normotensive kidney 
donors were pretreated i.v. with indomethacin 2
FIGURE 1. Blood pressure changes after kidney transplants. Types of transplantation experiments are denoted as follows. Left: (o o) SD recipient and SD donor; (x x) one-kidney, one-clip hypertensive recipient (1K1C) and SHR donor; (• •) 1K1C hypertensive recipient and SD donor. Initial blood pressure of the recipients in each group was 113 ± 8 (SEM), 182 ± 6, 189 ± 6 mm Hg, respectively. Right (o o) indicates WI-WI transplant, (x x) SHR-SHR transplant and (• •) transplant between SHR recipient and WI donor. Initial mean blood pressure in each group was 128 ± 2, 184 ± 5, 185 ± 2 mm Hg, respectively. Vertical lines at each point in graphic expresses the SE of the mean.

Discussion

This work confirms reports of others that the animal with experimental hypertension has a decline in BP when exposed to a kidney transplant whether such hypertension is initiated by renal artery clipping or Figure 8 ligation and nephrectomy,1-4 binephrectomy,5,6 DOC-salt administration,7,8 carotid denervation.9 In reviewing acute renal transplants into rats, the vasodepressor mechanisms appears to be primarily through a reduction in cardiac output.2,4 Since we consider the acute depressor effect of removing the renal artery clip in 1K1C hypertensive rats is mediated by a comparable mechanism, and since this experiment can be done in stages so as to avoid the cardio depressor effect of anesthesia, cardiac output determinations were performed in conscious rats before and after unclipping. The results are consistent with the conclusion of others, studying both conscious and anesthetized animals10 that the primary effect of un-
clipping is a decline in cardiac output. That the abrupt offset of hypertension does not involve a decline in total peripheral resistance at first seems paradoxical. It is possible that there is a later, secondary readjustment (autoregulation) which follows the decline in cardiac output.

Figure 2. Depressor effect of intrarenal (IR) infusions of constrictor agents on the transplant procedure. The line (o—o) = angiotensin II IR infusion (5 ng/kg/min), (x—x—x) = norepinephrine IR infusion (10 ng/kg/min), and (••) = saline IR infusion (0.02 ml/min). Recipients were SHR and donors WI rats. Initial mean blood pressure in each group was 182 ± 4, 183 ± 4, 185 ± 3 mm Hg, respectively.

Figure 3. BP change in unclipping experiments. Ordinate. BP change expressed in %. Mean initial BP of Group A = 194 ± 5 (SEM) mm Hg; Group B = 182 ± 7 mm Hg; Group C = 157 ± 8 mm Hg. Abscissa: Time in minutes for observation on BP in conscious, one-kidney, one clip hypertensive rats. Break in line extends for period of halothane anesthesia (25-45 min) during which clip was removed (Groups A and B) and in which a sham operation was performed (Group C). The second time period was in the postoperative, postanesthetic period. BP of Group A fell significantly (p < 0.001) from 50-120 minutes after unclipping. The reason for the nonresponse of Group B is unexplained, but it is presumed to be due to irreversible fibrosis at the site of the clip.

Figure 4. Percent changes in cardiac output. Initial cardiac output in ml/kg/min was for Group A = 311 ± 32 (SEM), Group B = 266 ± 18, and Group C = 317 ± 28. Other notations as in figure 3. P values in this and figure 3 denote differences with respect to Group C (* = p < 0.01, ** = p < 0.001).

There are a few known mechanisms for initiating a BP fall by an initial primary decline in cardiac output. DuCharme and McCandlis have described a venoconstrictor originating in the kidney. If this agent were augmented in hypertension and its release inhibited by...
exposure of a kidney to high perfusion pressure it could be a candidate for the unknown depressor secretion. A neural inhibitory mechanism could also be postulated which would act primarily on venous return and cardiac output, in the manner of ganglionic blocking agents. However, the carotid sinus reflex appears to be active in attempting to oppose the BP fall, at least in the unclipping experiment. Another possibility is the hormone postulated by Lucas and Floyer which is secreted by the kidney, and which facilitates the transfer of fluid into the interstitial space. This agent, if released by the perfused transplant or the unclipped kidney, would result in a decline in cardiac output and an increase in hematocrit. In the experiments reported above a small rise in the latter occurred but it was no less in the situations in which the BP did not fall and when the decline was prevented by infusion of saline the BP fall still occurred.

Despite the hemodynamic evidence against an immediate arterial dilator action, it seemed advisable to exclude as many known agents as possible. Indomethacin pretreatment excluded prostaglandin as mediator of transplant effect. The renal depressor lipid described by Muirhead’s group seems to be an unlikely candidate since it is reported to be an acute arterial dilator.

The 1K1C hypertensive animal is said to have “volume” hypertension and external loss of fluid is said to be a factor in the reversal. However, the BP fall after unclipping is noted when urinary loss of fluid is replaced. In this and previous work on the depressor effect of renal transplants external fluid loss by the donor kidney has been prevented without altering the depressor effect. Since an increased urinary loss by the recipient’s kidney (1K1C or SHR) has not been excluded and is hard to measure, we provided an infusion of saline of 1.5 ml over a 15-minute period to compensate for any hypothetical urinary fluid loss through the recipient’s kidneys, but a depressor effect of the procedure was still observed.

Evidence that a low concentration of angiotensin may inhibit the antihypertensive effect of the kidney has at least two logical consequences. It explains the failure of the normal kidney to lower the BP of an animal with acute renin-induced hypertension. It also may be the factor which keeps the “untouched kidney” in the two-kidney one clip hypertensive model from preventing the hypertension. Although such a kidney is exposed to a high perfusion pressure, its antihypertensive function is nevertheless inhibited by the rise in circulating angiotensin coming from the opposite, ischemic kidney.

Acknowledgment

The authors express their appreciation for the valuable work of Jean Gaymer (Ann Arbor, Michigan) and William M. Fraser and Jeffrey R. Roberts (Cleveland, Ohio). We also thank Dr. Mahesh C. Kholia, Dr. Subha Sen, and Dr. F. Merlyn Bumpus and the Cleveland Clinic Foundation for providing the laboratory facilities for the later phases of this work. Details of procedures, omitted for the sake of brevity, may be obtained by writing to the Research Division, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, Ohio 44106.

References

Antihypertensive effect of transplant of rat kidney or its unclipping. Hemodynamic effects and control mechanisms.
S W Hoobler, T Eto, R Welk and H Burge

Hypertension. 1981;3:II-200
doi: 10.1161/01.HYP.3.6_Pt_2.II-200

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1981 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/3/6_Pt_2/II-200

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension 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 Hypertension is online at:
http://hyper.ahajournals.org/subscriptions/