Direct Determination of Systemic Blood Pressure and Production of Hypertension in the Rabbit.* (26058)

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Repeated determinations of the blood pressure of the unanesthetized rabbit have been carried out in the past mainly by the indirect method of Grant and Rothschild(1), by means of an airtight capsule, applied to the ear, which permits visualization of the central artery. The pneumatic pressure required just to break the column of blood in this portion of the central artery, in systole, is taken as the systolic pressure in the artery. This pressure is lower than the direct mean pressure in the common carotid artery and is regarded by Grant and Rothschild merely as an "index" of systemic blood pressure. A number of disadvantages have interfered with the general use of this method, hence the rabbit has not been employed frequently in studies on experimental hypertension(2-5). One great drawback of this method is that the central artery must be in a state of dilatation, or at least not in constriction, for valid observations to be made, because a constricted artery gives lower values, and it is sometimes impossible to make a determination if the artery is greatly constricted. For this reason recent denervation of the ear is desirable, to avoid great fluctuations of the calibre of the central artery, which greatly modify the determination. If the ear is not denervated, or if the central artery has recovered from the effects of denervation, which often occurs within a few days, then to avoid changes in the calibre of the central artery, it is necessary to make all measurements in a very warm room, or to contrive to heat the whole rabbit, or at least the ear. It is also important always to apply the capsule to the same part of the central artery, because a variation of a few centimeters, toward the base or toward the tip of the ear, means a corresponding considerable increase or decrease, respectively, of blood pressure in the central artery.

Recently, during another study, it became necessary to use hypertensive rabbits, with repeated determinations of blood pressure of unanesthetized rabbits before and after surgical procedure for production of hypertension. Because of the drawbacks of the capsule method, it was desirable to develop a method of taking the blood pressure of the conscious rabit without carrying out determinations in a hot room, or heating or denervation of an ear. Having found the direct method reliable in determination of mean blood presure in the femoral artery of many unanesthetized dogs and other large animals(6), I decided to try this method on large rabbits.

Method for determination of blood pressure. Rabbits of different varieties, of both sexes, weighing from 3.5 to 5 kg were used. For direct determination of blood pressure in the femoral artery, the unanesthetized animal is placed in the supine position on a wooden trough, with both hind legs restrained lightly just above the ankles by wide leather straps tied to the sides of the board. The front legs may also be tied down, or preferably, an assistant† may hold the front legs and pull the animal up slightly to stretch the femoral artery somewhat. Once the animal is fixed and held on the board it usually remains remarkably quiet. It requires some skill, but with practice it is possible regularly, even several times daily if necessary, to insert a 22 gauge needle of ¾″ length through the skin into a femoral artery of a large unanesthetized rabbit. The needle is on the end of a glass cannula connected by plastic tubing to a mercury manometer of

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capillary bore. A large bottle containing normal saline solution, which can be subjected to pressure, communicates with the mercury manometer and with the tubing which leads to the needle. Manipulation of 2 stopcocks permits elevation of the pressure in the manometer and flushing of the glass cannula and needle. With the tip of the index finger of one hand in the groin, just below Poupart's ligament, the pulsating femoral artery is located, and this finger acts as a guide for the tip of the needle after it has been inserted through the skin and subcutaneous tissue. The needle is manipulated by the other hand which holds the glass cannula to which the needle is attached. It is important to use a sharp needle, to work slowly, and to push cephalad, gently, until the tip of the needle enters the artery. Successful puncture of the artery is signaled by the prompt entrance of a small amount of bright red blood into the cannula. If connection with the manometer is then established, by turning a stopcock, definite pulsation can be observed. The vein is so close to the artery, however, and both are of such small calibre, that occasionally the vein is punctured. This is easily recognized, because the blood is darker than arterial blood and because, if the stopcock is turned so as to connect the cannula with the manometer, the pressure in the manometer is very low and there is no pulsation. Puncture of the anterior crural nerve must be avoided and rarely occurs if the position of the nerve is kept in mind. After determination of the blood pressure has been made, the needle is withdrawn and pressure is applied at the site of puncture for a minute or more to prevent bleeding from the puncture in the skin or formation of a subcutaneous hematoma. If one does form, it may be expected to disappear in a few days, and the artery may then be punctured again at the same site. Clotting rarely occurs during the brief period of observation of blood pressure because, by proper arrangement of the 2 stopcocks in the system, it is possible to raise the level of the mercury in the manometer and flush out the cannula and needle. Neither thrombosis nor infection at site of puncture has occurred in any of the animals, although the skin is not sterilized and the needle, though clean, is not sterile.

TABLE I. Direct Mean Femoral Blood Pressure, mm Hg, of 24 Normal Rabbits Weekly for 3 Weeks.

Rabbit No.	Initial B.P.	8th day	15th day	22nd day
1	102	106	108	108
2	98	98	102	102
3	100	104	110	110
4	92	98	90	90
5	112	108	104	104
6	94	92	104	104
7	114	114	102	106
8	114	110	100	106
9	116	105	110	106
10	108	110	110	110
11	102	105	102	108
12	108	106	106	102
13	108	114	110	112
14	106	112	110	106
15	108	104	106	94
16	122	120	116	128
17	124	122	124	122
18	106	112	108	110
19	122	114	120	126
20	92	98	102	100
21	96	98	100	98
22	118	116	124	126
23	122	110	118	120
24	102	106	100	110

Blood pressure of normal rabbits. Table I gives direct mean femoral blood pressure, taken once a week, for 3 weeks, of 24 large, normal rabbits, of both sexes (mainly females), and different breeds (Chinchilla, New Zealand White, American Blue, Brown or Sandy), weighing from 3.3 to 5 kg. The relatively small variation from week to week in individual animals, and the slight differences between the animals are very striking. Table II shows blood pressures for 12 weeks of 3 female and 3 male Chinchilla rabbits weighing between 4 and 5 kg. In both Tables I and II the values are much more uniform than those that have been obtained by the indirect method of Grant and Rothschild(1-5).

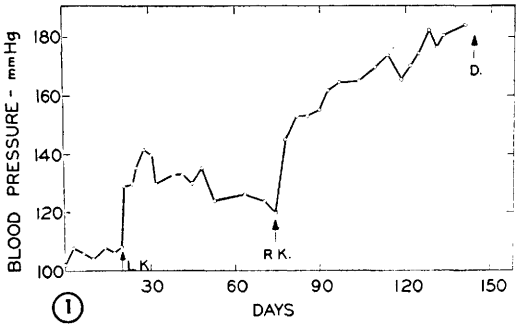
Production of experimental hypertension in the rabbit. Surgical procedure. The method for production of hypertension used in this study was constriction of both main renal arteries, or constriction of one main renal artery and contralateral nephrectomy(6). Because the diameter of the main renal artery of a rabbit weighing from 3.5 to 5 kg is so small, the type of silver clamp which was devised for constriction of the much larger arteries of

TABLE II. Direct Mean Femoral Blood Pressure, mm Hg, of 6 Rabbits Weekly for 12 Weeks.

Rabbit No. and sex	4/18	4/25	5/2	5/9	5/16	5/23	5/31	6/6	6/13	6/20	6/27	7/6	7/11
26 ♂	120	116	110	106	110	112	116	116	110	112	106	98	106
27 "	104	102	110	106	108	100	100	96	96	102	98	96	96
28 "	108	98	106	106	110	98	104	102	104	100	94	96	98
29 ♀	104	110	110	106	108	106	114	98	110	108	110	98	106
30 "	108	110	114	114	122	114	112	118	110	106	110	96	110
31 "	100	100	102	104	98	102	108	110	96	108	100	94	100

dogs weighing from 15 to 20 kg was not employed. The fashioning of a very small silver clamp of this type is difficult and too expensive. A silver ribbon clip was employed, of the type used for the rat(7), but made from a silver ribbon 0.25 cm in width and 0.8 cm in length. The ribbon is bent at its middle over a round wire 0.15 cm in diameter and one free edge is turned up slightly to facilitate handling with forceps. As in the dog, for isolation of a part of the renal artery, the retroperitoneal approach is used, and the operation is carried out through an oblique lateral abdominal incision, just below and parallel to the costal margin, beginning at the costolumbar angle. The muscles are split in the direction of their fibers and, during splitting of the transversalis muscle, special care is taken not to puncture or tear the peritoneum which is stripped away from the lumbar muscles by means of a finger tip. A small self-retaining retractor is then inserted through the wound. The kidney and main renal artery are easily identified. The first part of the main renal artery is dissected free and cleaned for about 1 cm or less from its origin in the aorta. The artery is lifted by means of a metal hook into the rounded part of the clip and is then completely enclosed in the clip by pinching together the free edges. For production of the desired degree of constriction of the artery by the silver clip, a special forceps devised in our laboratory for the rat(8) has proved useful. By means of this forceps degree of constriction of the artery can be varied at will. Once the vessel is enclosed in the clip, the entire clip is squeezed in the jaws of the forceps to the limit permitted by the previous setting of the screw for separation of the jaws(8).

Results of constriction of one or both main renal arteries. In some of the rabbits the degree of constriction proved too great, so that the kidneys became partly or completely necrotic. When this occurred bilaterally, fatal uremia, usually accompanied by hypertension, quickly developed. In other animals, when the arteries were not adequately constricted, there was no elevation of blood pressure. By trial and error, however, it was found that a gap of 0.030″ to 0.032″ between the jaws of the forceps gave the right degree of constriction of the main renal artery of a rabbit weighting between 3.5 and 4 kg, while 0.034″ to 0.036″ was best for a rabbit weighing between 4.5 and 5 kg. Fig. 1 and 2 show the blood pressure records of 2 rabbits before and after constriction of first one and then the other main renal artery. Peart(9) has stated that, "without an elevation of blood urea no elevation of blood pressure occurs in rabbits." This was undoubtedly true for his rabbits, but that it is not applicable to all rabbits, is shown by Rabbit No. 25, (Fig. 2), in which blood urea, creatinine and non-protein nitrogen remained well within the limits of normal throughout the entire period of the considerably elevated blood pressure. The reason for the occurrence of impairment of renal excretory function in the rabbit more frequently than in the dog is that it is more difficult to avoid excessive constriction of the main renal artery in the rabbit, and uremia is especially likely to occur if the artery of one kidney is constricted and the other kidney is removed. This is a good method for production of persistent hypertension, in the dog, but hazardous in the rabbit in which it is better to constrict both main renal arteries, with an interval of a week or more between operations. Fig. 1 and 2 illustrate the results of the latter procedure in 2 rabbits. In



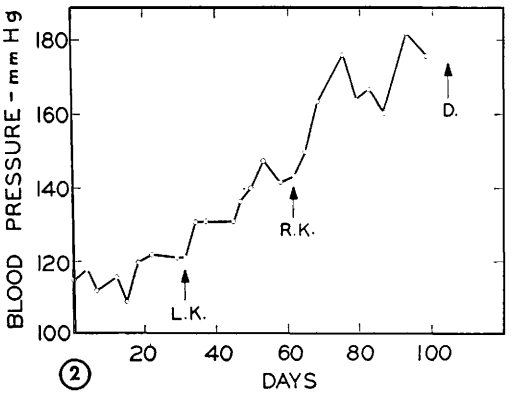


FIG. 1. Rabbit No. 1. L.K., moderate constriction of left main renal artery. R.K., moderate constriction of right main renal artery.

FIG. 2. Rabbit No. 25. L.K., moderate constriction of left main renal artery. R.K., moderate constriction of right main renal artery.

Rabbit No. 1 (Fig. 1) blood pressure was returning to the original level before the right main renal artery was constricted, 8 weeks after constriction of the left, while in Rabbit No. 25 (Fig. 2) blood pressure was still rising when the right was constricted 30 days after constriction of the left main renal artery. In both animals blood pressure rose appreciably after constriction of the first main renal artery, but became much more persistently elevated, after constriction of the second. Both animals died unexpectedly, and the only abnormalities found at autopsy were dilatation of the chambers of the heart and moderate edema of the lungs. In Rabbit No. 1 (Fig. 1) no chemical determinations of the blood were made, but in Rabbit No. 25 (Fig. 2) blood urea nitrogen, creatinine and non-protein nitrogen values remained unchanged after constriction of both arteries and development of persistently elevated blood pressure. Other hypertensive rabbits have also failed to show significant alteration of renal excretory function.

Summary. A method is described for determination of direct mean systemic blood pressure in the femoral artery of the unanesthetized rabbit. Weekly blood pressures of 24 rabbits, for 3 successive weeks, and of 6 other rabbits, for 12 weeks, are given. Production of persistent renal hypertension, unaccompanied by significant impairment of renal excretory function, is described and illustrated. It is hoped that publication of this method for determination of the blood pressure of the unanesthetized rabbit will stimulate others to employ this animal more often in future studies of experimental hypertension.

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