Hemodynamic Changes in Trained Dogs During Experimental Renal Hypertension

By Frederick Olmsted, B.A., and Irvine H. Page, M.D.

To provide better understanding of cardiovascular mechanisms involved in the onset and maintenance of experimental renal hypertension, we have applied improved techniques of measuring cardiac output and arterial pressure in conscious dogs. This has been done by implanting a flow probe on the ascending aorta and a catheter in the aortic arch.1 Well trained dogs, allowed freedom of movement so that they were in an essentially normal state, were the subjects of experiment. We have determined, in detail, the series of hemodynamic events accompanying the hypertension that follows partial constriction of one renal artery and unilateral nephrectomy.

Data on the hemodynamic status of experimental renal hypertension are scarce. Single determinations by the Fick method in anesthetized dogs with established renal hypertension by Holman and Page2 have shown cardiac output to be normal and peripheral resistance raised. Recently, Ledingham and Cohen3 found cardiac output increased in conscious rats at the onset of experimental renal hypertension. After several days it returned to normal.

Methods

Mongrel dogs weighing from 17.5 to 24 kg were prepared, using anesthesia and aseptic technique, by implanting a flow probe around the ascending aorta, and a catheter in the aortic arch. Terminals of the flow probe cable and a stopcock on the catheter were incorporated into skin buttons4 and exteriorized at the back of the neck. In two dogs catheters only were implanted. A week later, control recordings and training were started. Training consisted of having the dogs lie on a soft pad while connected to the recording equipment. Connections were made5 by means of a plug in the flow probe skin button and cables to a phase detection electromagnetic flowmeter.* A short plastic tube from the arterial catheter led to a pressure transducer† which was fastened at heart level to a shoulder harness worn by the dogs. Cables to the dogs were flexible and long enough so that no restraint was needed, and under these conditions the animals became accustomed to lying quietly in one place. Training was considered finished when the dogs, upon entering the laboratory, went of their own accord to the soft pad and reclined upon it. After training was complete, experimental renal hypertension was induced by partially constricting the left renal artery by a Goldblatt clamp; at the same operation unilateral nephrectomy was done.

Measurements were (fig. 1, channels from top down): 1) instantaneous flow velocity in the ascending aorta, and 2) blood pressure in the aortic arch. From the two values, pressure and flow, factors derived by electronic analog circuits were: 3) stroke volume and cardiac output, 4) mean arterial pressure, 5) integrated heart rate, and 6) peripheral resistance. These six channels of information were recorded by a rectilinear multichannel recorder of adequate frequency response.* Recordings were made at least once daily for 20 to 30 minutes, usually at the same time of day. Data were not taken from the tracings until all values had been stable for several minutes.

Tracings were made at a chart speed of 50 mm/sec to record waveforms, and at 5 to 15 mm/min for typical resting levels from day to day. Blood pressure was read to the nearest 5 mm Hg, cardiac output to the nearest 50 ml/min, heart rate to within 5 beats/min, stroke volume to within 1 ml, and mean arterial pressure to 2 mm Hg. Peripheral resistance was calculated in percentage change, from control level, of arbitrary values on the tracing obtained from the quotient of mean arterial pressure/flow, at four-second intervals.

*Electronic Specialties, Inc., Cleveland 24, Ohio.
†Statham P23d.
*Sanborn 150 Series.

From the Research Division of the Cleveland Clinic Foundation, Cleveland, Ohio.

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By the fourth day of training the values for hemodynamic factors tended to stabilize at levels lower than those first recorded. Hence, results obtained on the fourth and fifth days of training, or later, were taken as control values.

Results

Thirty-four dogs were prepared by implanting flow transducers and catheters and, after a week of kennel rest, subjected to training for at least five days. Next, in 26 of these a renal artery was constricted and unilateral nephrectomy done. Nineteen of the dogs were successfully made hypertensive by this procedure, while in seven there was no change of blood pressure. The latter served as controls for possible effects of the operative procedure on hemodynamic status. Control periods of five to seven days were followed by studies of hypertension lasting four to forty-two days.

The left section of figure 1 shows a typical control tracing at the conclusion of training. The ventricular ejection curves were regularly spaced and similar in size. Mean arterial pressure was 80 to 90 mm Hg and heart rate was well below 100/min. Peripheral resistance was low, and cardiac output was 3 liters/min in this 22-kg dog. Figure 2 shows the grouped values of control studies in the 34 dogs before initiation of hypertension. Heart rates did not exceed 95 beats/min, and few mean pressures were above 100 mm Hg.

The right section of figure 1 shows changes in the same dog two days after constriction of a renal artery and unilateral nephrectomy. The flow curves were unevenly spaced, and
varied in size. Arterial pressure was elevated, the mean being 60 to 70 mm Hg above control values. Heart rate was reduced and peripheral resistance increased. Cardiac output was reduced markedly, and the pulse pressure was increased, with the dicrotic notch displaced on the curve from its control position.

Figure 2 shows the grouped values (means, ranges, significance) in 19 dogs measured one to four days after constriction of a renal artery and contralateral nephrectomy. The average rise in mean arterial pressure was moderate at 35 mm Hg, with definite decreases of cardiac output and heart rate that amounted to 20% or more of control values, while peripheral resistance was sharply elevated. Stroke volume did not change significantly. Thus, during the first few days there was a rise of arterial pressure, accompanied by decrease of cardiac output and heart rate, and elevation of peripheral resistance. In the seven dogs, in which renal artery clamping and contralateral nephrectomy did not affect arterial pressure, the hemodynamic state was not altered significantly.

Between the tenth and twentieth day after constriction of a renal artery a relatively stable chronic state was attained. Arterial pressure ceased to increase (except in two instances of "malignant" hypertension). Cardiac output and heart rate had returned essentially to normal. Following the period of onset of one to four days, arterial pressure and peripheral resistance gradually increased to attain a maximum on the tenth to twentieth days, after which time elevation was maintained at a plateau for as long as 42 days. Figure 2 shows values for the chronic state. Mean arterial pressure averaged 65 mm Hg (range 52 to 92 mm Hg) above control value.

The progression from initial, acute hypertension to the chronic stage was not even. As previously observed in normal dogs, the contributions of cardiac output and peripheral resistance to maintenance of a steady arterial pressure varied in ratio to each other, and these variations were accompanied by changes of heart rate. In the renal hypertensive dog variability was increased at this time, and an instance of this is seen in figure 3. Between the left and middle sections of the record, made on the twelfth and thirteenth days after initiation of pressure rise, without change in mean arterial pressure, cardiac output and heart rate increased, while peripheral resistance decreased slightly. The pulse pressure contour was also altered, changing from an angular peaked form, often present when peripheral resistance was great-

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**FIGURE 2**

Averages and ranges during stable control periods, onset of hypertension, and chronic hypertension. The control segment at the left is calculated from 58 recordings in 34 dogs. Solid vertical bar (arrow) indicates when renal artery constriction and unilateral nephrectomy were done. Displaying values are in percent change from average control value, except for pressure, which is shown throughout in mm Hg. Results under "onset" of hypertension are derived from 36 recordings from 19 dogs. Decreases of cardiac output and heart rate are obvious, as is the large and acute increase of peripheral resistance. The rise of blood pressure to a stable elevation in the chronic state is accompanied by further increase of peripheral resistance and return of cardiac output and heart rate to near control levels. The significance of changes after initiation of hypertension is $P < 0.001$. This is true also for changes from "onset" to chronic hypertension except for peripheral resistance between onset and the chronic state, where $P \leq 0.005$. 

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Two sections to left show the transition between the state of hypertension on the twelfth day after constriction of a renal artery and the chronic state appearing on the thirteenth day. Although mean arterial pressure is unchanged, heart rate and cardiac output are increased, peripheral resistance is slightly lower, and pulse pressure is modified. The right section shows a malignant phase of hypertension; note change in pressure scales. Diastolic pressure sometimes exceeds 150 mm Hg. The pulse pressure contour is triangular, the dicrotic notch almost at peak of systole. Heart rate is again slowed. The change of pressure scale gives the recorded peripheral resistance a value 20% higher than in the two sections to the left.

A malignant phase of hypertension appeared occasionally, either after several weeks, or as early as three to four days after the first rise in blood pressure (e.g., right side of fig. 3). Arterial pressure was extremely high; the diastolic pressure was 150 mm Hg and sometimes higher, while mean pressure was about 195 mm Hg. Cardiac output and heart rate were sharply reduced, and peripheral resistance was the highest observed in this study. The pulse pressure contour was again angular and peaked. If the malignant phase appeared during the first few days of hypertension, it could often be reversed by loosening the renal artery clamp. At this time, 28 days after constriction of a renal artery and unilateral nephrectomy, the blood urea concentration was 306 mg/100 ml, indicating severe renal impairment. This dog died in a few days with blood urea of 378 mg/100 ml. Pathological changes were focal retinal hemorrhages and exudates, and in the kidney, acute tubular necrosis with focal interlobular hemorrhages.

Discussion

The average control arterial pressure of the 34 dogs, recorded when they were lying quietly, was 119/68 mm Hg; the average mean pressure was 85 mm Hg. This is significantly lower than normal levels reported in unanesthetized dogs in the past. Goldblatt\textsuperscript{7} found that mean pressure measured by femoral arterial puncture, in trained dogs, ranged between 120 and 140 mm Hg. By Van Leersum loop technique, he found systolic pressures as high as 170 to 180 mm Hg in normal dogs. Hamilton et al.\textsuperscript{8} used femoral artery puncture...
to measure pressures of 215 untrained street dogs sedated by morphine, and found an average pressure of 180/89 mm Hg. In two trained dogs without sedation the arterial pressure was no lower. Gregg, Eckstein, and Fineberg\(^9\) used needle puncture of a carotid artery in a Van Leersum loop in trained, reclining dogs. Average pressure was 124/85 mm Hg. McCubbin and Corcoran\(^10\) by direct femoral artery technique, found an average mean pressure of 130 mm Hg in untrained street dogs.

Although systolic pressure in the femoral artery may be 40 mm higher than in the aortic arch, diastolic and mean pressures are the same.\(^11\) Mean pressure can be derived approximately from pulsatile pressure (diastolic + 1/3 pulse pressure). The lowest mean pressure reported above is then 98 mm Hg (Gregg, Eckstein, and Fineberg) and this is 13 mm Hg above the mean pressures in our dogs, which averaged 30% lower than those described above.

The pressures closest to ours were measured in trained, reclining dogs, while most of the remainder were determined in dogs lying on their backs to expose the femoral artery for needle puncture.

In addition to the catheters in the aortic arch, our dogs had the rigid sleeves of flow probes fitting, but not constricting, the ascending aorta. To determine if implantation of flow probes influenced blood pressure, two dogs in which only aortic arch catheters had been placed, were subjected to the same test procedures as the others. Following thoracotomy they were given a week of kennel rest for recovery, and then five days of training while recording blood pressure. At the start of training their pressures were 152/76 and 152/88 mm Hg, with respective means of 113 and 124 mm Hg. On the fifth day of training, pressures had fallen to 116/60 and 120/70 mm Hg, and the means were 85 and 88 mm Hg. Thus, in these dogs the same low arterial pressures were reached as in the other dogs, and this appears to be due to training and handling of the animals and to the reclining position that they naturally assumed. The flow probes did not alter arterial blood pressure.

Ledingham and Cohen\(^8\), using an implanted electromagnetic flow probe, found increased cardiac output and decreased heart rate in unanesthetized rats at onset of experimental renal hypertension. Therefore, stroke volume must have been increased. We found no significant change in stroke volume in our dogs at any stage of renal hypertension. The rat's normal heart rate can reach at least 400 beats/min. The left ventricular ejection curve might then attain its systolic peak, assuming their waveform is comparable to the dog's, in 5 to 8 msec. Under these circumstances, results from the variety of present electromagnetic flowmeters must be evaluated with great care.

It is evident that at the onset of hypertension cardiovascular functions must be disturbed profoundly. Systemic blood flow is reduced significantly below normal, apparently through pressor receptor reflex arcs which reduce heart rate. With passage of time, and in spite of continued increase of arterial pressure, adaptations of cardiovascular control mechanisms\(^12\) act to restore blood flow to normal. These mechanisms can again be disturbed by further elevations of blood pressure found in the "malignant" phase of experimental renal hypertension. The acute decrease in cardiac output at the onset seems a part of this experimental disease, since no such changes occurred in the seven control dogs in which the renal artery was not constricted enough to cause any rise in arterial pressure. The main circulatory change in chronic experimental renal hypertension is elevation of peripheral resistance as originally found by Holman and Page\(^2\) using the Fick method.

As previously described\(^4,13\) the flow probes were calibrated with known steady flows of saline and blood through an artery in the lumen of the probe. Sometimes they were calibrated in the dog's chest after implantation, followed by later sacrifice of the animal. Day to day calibrations did not vary more than ±2%. In the phase detection method used.
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there is no critical electrical balance, and the probes are stable in sensitivity. Frequency response was also adequate. 13

Summary

The hemodynamic events, during onset of experimental renal hypertension, and during its progression to the chronic state, were recorded in 19 trained quiet dogs for 20 to 30 minutes daily for four to forty-two days. This was made possible by implanting a flow probe around the root of the aorta, and a catheter in the aortic arch for connection to an external pressure gauge. Continuous graphic recordings of blood pressure, cardiac output, stroke volume, heart rate, and peripheral resistance were made daily during a period of training to obtain control values, and after hypertension was initiated by partial occlusion of a renal artery and unilateral nephrectomy.

The average mean arterial pressure in 34 unanesthetized dogs in this study was 85 mm Hg (range, 68 to 116 mm Hg). This is about 30% below values previously reported by others in unanesthetized dogs. These low pressures were ascribed to lack of restraint, to training, and to the natural posture of the dogs.

At onset of hypertension a sharp rise in arterial pressure was accompanied by a decrease of cardiac output and heart rate, and by a large abrupt increase of peripheral resistance.

After one to four days, the continued rise of arterial pressure was associated with return of cardiac output and heart rate toward normal. Peripheral resistance eventually stabilized at a level above that of the initial large rise. A chronic state of hypertension was reached by ten to twenty days after the initial rise of pressure. At this time cardiac output and heart rate were restored to normal, while peripheral resistance remained elevated. Studies lasting for as long as forty-two days did not show further changes.

If the renal arterial constriction was severe, a third, "malignant" phase ensued with extreme elevation of diastolic pressure, reduction of cardiac output, and greatly increased peripheral resistance. This terminated in uremic death after a few days.

References

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