Changes in Cardiac Output and Total Peripheral Resistance during Development of Renal Hypertension in the Rabbit

Lack of Conformity with the Autoregulation Theory

PETER J. FLETCHER, M.B., PAUL I. KORNER, M.D., JAMES A. ANGUS, PH.D., AND JUDITH R. OLIVER

SUMMARY Serial measurements of cardiac output (CO), mean arterial pressure (MAP), heart rate, and total peripheral resistance (TPR), were made on unanesthetized rabbits with previously implanted Doppler flowmeters. After 2 days of control measurements the rabbits were subjected alternatively to bilateral renal cellophane wrapping (wrap group) or to sham operation and additional measurements were made 1, 2, 4, 8, 16, 25, and 32 days after operation. During the 1st week after operation changes in CO were identical in the wrap and sham-operated groups, with an overall increase to a value of 110% of control on day 4 ($P < 0.05$). Thereafter CO fell gradually, reaching 75% of control by day 32 in the wrap group, but only 95% of control in the sham-operated group. When CO was expressed per unit of body weight the latter differences were somewhat reduced, but still were significant. In wrap animals MAP and TPR rose progressively to 155% and 194% of control by day 32. In the sham-operated group the corresponding increases to 108% and 118% of control were significantly smaller. The MAP and TPR of the renal wrap rabbits exceeded the values in sham-operated rabbits, even over the 1st week after operation, by an average for MAP of 8.6 ± 1.4% ($P < 0.001$), and for TPR of 8.0 ± 2.5% ($P = 0.01$). The results suggest that the changes in CO during the 1st week were a nonspecific consequence of the preceding wrap or sham operation. They bore no apparent relationship to the subsequent development of the hypertension which was "resistance-mediated" from the earliest stages. We conclude that the present findings for the rabbit differ from those reported for other species and do not conform to the changes predicted by the autoregulation theory of the pathogenesis of hypertension.

IN SEVERAL recent studies a phase of high cardiac output (CO) early in the development of experimental hypertension has been reported. The subsequent elevation in blood pressure has been associated with a progressive increase in vascular resistance and a restoration of the CO to control values. Ledingham and Cohen first suggested that the rise in vascular resistance might be the result of autoregulation of tissue blood flow that was inappropriately high in relation to the tissue metabolic needs. The hemodynamic pattern described here has been observed in several types of hypertension, including experimental renal hypertension. Moreover, in some of the studies reporting an increase in output the interpretation of the data has been complicated by the absence of a control group of normotensive animals to assess any nonspecific effects of the experimental procedures used. Our present study was undertaken to compare the hemodynamic patterns occurring during the development of renal wrap hypertension in rabbits (in which changes in CO have not been studied to date) with those found in a similar group of sham-operated rabbits.

Methods

ANIMALS AND OPERATIONS

Male New Zealand White rabbits (mean body weight, 2.5 kg; range, 2.3–2.9 kg) were used for these experiments. Two preliminary operations were performed under open circuit halothane anesthesia, following induction with propanidid (Eptonol, Bayer), approximately 30 mg/kg, i.v. First, a Doppler ultrasonic cuff-type blood flow transducer [inner diameter (i.d.) = 5 mm] was placed around the ascending aorta through a thoracotomy in the 2nd left intercostal space. The wires were buried subcutaneously in the dorsal midline. At the second operation, performed 7–10 days later, these wires were led subcutaneously along the back of the neck and soldered to a plug subsequently attached to the rabbit’s skull with dental acrylic; this facilitated the subsequent measurement of CO. In some rabbits the wires broke at the back of the neck after about 3–4 weeks, but usually could be recovered by a small cutdown under local anesthesia on the day of the study. The rabbits recovered well from these procedures; criteria for entry into the study were that the rabbits were in good general condition, with no evidence of infection and with adequate wound healing and stable weight or weight gain.

After the control measurements (see Protocol and Mea-
measurements, day 0) the rabbits again were anesthetized with propanidid-halothane. Renal wrapping or sham operation was performed in alternate rabbits. Both kidneys were exposed through flank incisions and were wrapped in cellophane in one group of rabbits. The renal fat was separated from the capsule, the kidney was mobilized, and a cellophane square (approximately 12.5 x 12.5 cm^2) was wrapped around the kidney, with the ends gathered at the hilum and secured loosely with a silk tie. In a second group of rabbits we performed a sham operation in which the kidneys were exposed retroperitoneally but were not disturbed. Each procedure lasted 30-40 minutes, and the rabbits had recovered from the effects of anesthesia within half an hour after the termination of surgery.

**PROTOCOL AND MEASUREMENTS**

Each rabbit was studied on 2 control days. The 1st day was at least a week after the “head-plug” operation, and the 2nd day was 2-3 days later. On day 0 alternate rabbits were allocated to the renal wrap or sham-operated groups. Because of the limited number of ear artery cannulations we could do in each rabbit, we studied two series of rabbits. In series A the changes occurring on days 1, 2, 4, and 8 after operation were studied in seven wrap and seven sham-operated rabbits. In series B we studied the changes occurring on days 4, 8, 16, 25, and 32 after operation in 10 wrap and nine sham-operated rabbits. Four wrap and three sham-operated rabbits were common to both series.

On each day of study a polyethylene SP 10 catheter was inserted into the central ear artery under 0.5% lidocaine local anesthesia. The rabbit was connected to the flowmeter assembly and placed in a rabbit box in which it rested for approximately 1 hour before the start of recording. Arterial pressure (P23D Statham strain gauge) (mm Hg), heart rate (beats/min), ascending aortic blood flow (kHz Doppler shift, see below) and total peripheral resistance (TPR), calculated as the ratio of mean arterial pressure (MAP) to mean aortic blood flow, were recorded on a Grass polygraph. On each day we took continuous recordings during four separate 5-minute periods separated by 5-10 minutes during which the calibrations were checked and the flowmeter retuned (see below). For each 5-minute period, estimates of CO (mean aortic blood flow), heart rate, MAP, and TPR were obtained, each as a mean of 14 equispaced readings. The overall mean of the four period means was the final estimate of each variable on any 1 day.

**DOPPLER ULTRASONIC FLOWMETER**

The flowmeter consisted of a cuff transducer (i.d. = 5 mm), a flowmeter (oscillator and receiver unit), an audio unit which was in parallel with a 200-Hz to 50-kHz band pass filter, a frequency to voltage (F-V) converter, and 100-Hz low pass filter (Pierson Laboratories), as described previously.18 In previous studies from our laboratory West et al.19 showed in pump-calibration experiments that under conditions similar to those of the present study the relationship between volume flow and Doppler shift was linear and was not altered by substantial changes in perfusion pressure, indicating that the cuff transducer had become firmly adherent to the underlying vessel. However, in their study the slopes of the regression lines differed significantly between individual transducers. This may have been because the transducer shells were loose when applied to the aorta at the first operation19 and this may result in small differences in orientation between transducer crystals and axis of the vessel that cause differences in sensitivity. These differences between transducers of a given inner diameter appeared to be randomly distributed about a mean value, since the means of the individual slope values and the calibration lines calculated from the pooled data of each of two different groups of rabbits were closely similar.18 The calibration did not alter in chronic hypertension. These calibration studies indicate that the Doppler method can be used to accurately determine changes in volume flow in a given animal; moreover, in a given group of animals the mean absolute volume flow is related with moderate accuracy to the mean of the Doppler shifts of the individual rabbits. The accuracy of measuring changes in CO was similar to that observed with the electromagnetic flowmeter.18 The Doppler instrument is unidirectional and registers the 3-4% of backflow occurring early in diastole19 as a small additional forward deflection which has been neglected in our present study.

In the present study the upper frequency limit of the band pass filter was set at approximately twice peak aortic velocity to prevent signal attenuation. The sensitivity of the F-V converter was adjusted so that late diastolic flow was set at electrical zero. The validity of this setting was confirmed in several experiments in which diastole was greatly prolonged after rapid intravenous injection of 100 μg acetylcholine.

In 10 rabbits not used in the main study, calibration in vivo of the Doppler assembly was performed with the thermodilution method as a reference.18 With the tuning of the Doppler flowmeter left unaltered through the experiment, CO was compared in each rabbit (1) under control conditions; (2) at low output levels obtained by infusing the ganglion-blocking drug trimethaphan camsylate (4 mg/min, iv); (3) at high output levels obtained by infusing mixture of isoprenaline (0.5-1.0 μg/min) and papaverine (4 mg/min, iv) in 0.9% NaCl. In each rabbit changes in flow could be determined accurately because the relationship between Doppler shift and thermodilution CO was linear (Fig. 1), in agreement with the pump-calibration data. In the present study again there were significant differences between the slopes of the calibration lines of individual transducers (Fig. 1). To investigate the reproducibility of each calibration line with repeated tuning of the instrument we repeated the calibration in five rabbits 1 week after the first study, i.e., with the entire assembly retuned. In none of these was there any significant difference in the slopes on the 2 days, but in some there was a small but significant change in the intercept. The latter may have resulted from a small amount of systolic noise associated with slightly suboptimal tuning of the flowmeter on any particular occasion. The variation in intercept appeared to be randomly distributed because the mean difference in intercept within the five rabbits on the 2 days was 0.15 ± 0.13 kHz, i.e., not significantly different from zero.

To minimize systematic effects on the intercept due to tuning errors we retuned the flowmeter four times on each day of the study with 14 flow measurements obtained over a
5-minute period at each tuning. Analysis of variance was performed for the hypertensive and normotensive rabbits from the data of individual tunings on the 2nd control day and postoperative days 4 and 25. There was no significant difference in the residual within-animal tuning error between the two groups and no systematic time trends between tunings in each group. The standard deviation due to tuning error was ±0.15 kHz, i.e., approximately ±4% of the mean Doppler shift. This is of the same order of magnitude as the small intercept differences between tunings in the calibration experiments. If one assumes that the tuning errors are randomly distributed, the standard error of the mean due to tuning errors was reduced from ±4% of the mean Doppler shift following a single tuning to ±2% of the mean Doppler shift after the four separate tunings of the present protocol.

STATISTICAL ANALYSIS

The significance of the changes on the various days in the different circulatory variables was assessed where appropriate by the paired t-test and by analysis of variance. In analyzing data such as those in Table 1, showing the early postoperative CO changes in series A, the total sums of squares (SS) were partitioned into the following groups: SS between rabbits, SS between days, and SS error. The SS between rabbits was partitioned into SS between groups (wrap vs. sham) and SS between rabbits within each group. The SS between days was partitioned according to the following three orthogonal comparisons: difference between average of days 1 and 2 and average of days 4 and 8; difference between day 1 and day 2; difference between day 4 and day 8. The remaining sums of squares were partitioned into groups × days interaction and residual error. Statistical analysis was performed both on the percentage changes from control and on the absolute changes in each variable, and there were no important differences in the statistical significance of the results obtained.

Results

CONTROL VALUES

The absolute mean control values before renal wrapping or sham operation were similar for series A and series B (Table 2). Differences in the hemodynamic variables for any one rabbit on the 2 control days and in heart rate were small and were not statistically significant (Figs. 2 and 3).

Early Postoperative Changes

During the 1st week after operation the changes in CO were similar in renal wrap and sham-operated rabbits, but in each group there was a considerable variation in individual responses (Table 1, Figs. 2 and 3). In series A the CO fell in each group on day 2 after operation to an overall mean for each group there was a considerable variation in individual rabbits. We analyzed the frequency with which a particular change in CO occurred on days 4 and 8, using all 26 rabbits from both series A and B (Table 3). In both the wrap and sham-operated groups about half the rabbits showed a rise greater than 5% from control. The remainder either showed no change or slowed a fall by more than 5% (Table 3). The proportion of rabbits showing any given type of change was not significantly different in wrap or sham-operated rabbits (x^2 = 1.78, 2 degrees of freedom (df)). When we examined the data from the 13 renal wrap rabbits and the 13 sham-operated rabbits on days 4 and 8 on an in-

<table>
<thead>
<tr>
<th>Rabbit</th>
<th>CO (% of control)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wrap group</td>
<td>Day 1</td>
</tr>
<tr>
<td>1</td>
<td>105</td>
</tr>
<tr>
<td>2</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>89</td>
</tr>
<tr>
<td>4</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>88</td>
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<tr>
<td>6</td>
<td>106</td>
</tr>
<tr>
<td>7</td>
<td>97</td>
</tr>
<tr>
<td>Mean</td>
<td>92.7</td>
</tr>
</tbody>
</table>

Sham-operated group

<table>
<thead>
<tr>
<th>Rabbit</th>
<th>CO (% of control)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>89</td>
</tr>
<tr>
<td>9</td>
<td>89</td>
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<tr>
<td>10</td>
<td>129</td>
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<tr>
<td>11</td>
<td>90</td>
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<td>12</td>
<td>77</td>
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<td>13</td>
<td>94</td>
</tr>
<tr>
<td>14</td>
<td>94</td>
</tr>
<tr>
<td>Mean</td>
<td>94.6</td>
</tr>
</tbody>
</table>

Overall mean | 93.6 | 101.6 | 109.5 | 106.7 |

* Results are expressed as the percentage of each rabbit's average control values.
TABLE 2  Mean Control Values

<table>
<thead>
<tr>
<th>Variable</th>
<th>Series*</th>
<th>Wrap group</th>
<th>Sham-operated group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Output (kHz)</td>
<td>A</td>
<td>3.62 ± 0.37</td>
<td>3.97 ± 0.22</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>4.05 ± 0.30</td>
<td>4.14 ± 0.27</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>A</td>
<td>255.6 ± 4.46</td>
<td>253.1 ± 15.99</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>246.5 ± 8.82</td>
<td>242.4 ± 6.03</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>A</td>
<td>84.4 ± 2.43</td>
<td>84.4 ± 2.29</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>80.8 ± 1.46</td>
<td>85.4 ± 1.66</td>
</tr>
<tr>
<td>Total peripheral resistance (mm Hg/kHz)</td>
<td>A</td>
<td>10.47 ± 1.13</td>
<td>9.07 ± 0.58</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>9.19 ± 0.68</td>
<td>8.78 ± 0.57</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SEM.

* In series A, number of rabbits = 7 wrap, 7 sham-operated; in series B, 10 wrap, 9 sham-operated.

In individual basis there was no correlation in either group between the changes in CO and the changes in MAP.

Heart rate changes were small and variable, with the exception of a rise to 113% in the wrap animals on day 1 after operation (difference from sham groups = 11 ± 4.2%, P < 0.05). The stroke volume was slightly lower in the wrap than in the sham-operated rabbits during the first 2 days after operation, but on days 4 and 8 when the increase in CO was maximal the increase in stroke volume was maximal in each group. On these days the increase in CO was accounted for entirely by the stroke volume changes.

In contrast to the absence of any differences in CO responses between wrap and sham-operated groups, the differences in MAP and TPR responses, though small, were statistically significant (Figs. 2 and 4, series A). Thus MAP of the wrap rabbits in series A significantly exceeded that of the sham-operated rabbits on postoperative days 1, 2, and 8.

The mean difference between wrap and sham-operated rabbits over the

**TABLE 3**  Frequency of Cardiac Output (CO) Changes on Days 4 and 8 after Renal Wrap or Sham Operation

<table>
<thead>
<tr>
<th>CO changes (no. of rabbits)</th>
<th>&gt;5% rise</th>
<th>±5%</th>
<th>&gt;5% fall</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wrap group</td>
<td>6</td>
<td>4</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>Sham-operated group</td>
<td>6</td>
<td>7</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>Total*</td>
<td>12</td>
<td>11</td>
<td>3</td>
<td>26</td>
</tr>
</tbody>
</table>

* χ² = 1.78; 2 degrees of freedom (df): 0.25 < P < 0.5, using correction for discontinuity.

* Total was 26 rather than 33 rabbits, since 4 wrap and 3 sham-operated rabbits were common to both series A and B.
HEMODYNAMIC CHANGES IN HYPERTENSION/Fletcher et al.

FIGURE 4 Changes expressed as percent of average control in mean cardiac output (CO), heart rate (HR), mean arterial pressure (MAP), and total peripheral resistance (TPR) in series A and series B. Thick lines and solid circles = renal wrap rabbits. Interrupted lines and open circles = sham-operated rabbits. Error bar to the left of control (C) values is ± 1 standard error of difference between means of wrap and sham groups derived from analysis of variance. Asterisk (*) indicates a significant difference (P < 0.05) between wrap and sham groups.

The changes in heart rate with time were small in each group and did not differ significantly. Stroke volume tended to be somewhat lower in the wrap group as compared to sham-operated rabbits, but the difference was significant only on day 32 (−16.9 ± 3.9%; P < 0.001).

Lack of correlation between CO changes in the first few days after wrapping and subsequent development of hypertension is further suggested from the variability in early CO responses in individual rabbits within the wrap group. For example, in two wrap rabbits MAP and TPR rose at about the same rate and reached similar values by day 32, although in one rabbit there had been a significant “early” elevation in CO above control while in the other there had not; in both, CO was significantly below control by day 32 (Fig. 5).

FIGURE 5 Changes in cardiac output (CO), mean arterial pressure (MAP) and total peripheral resistance (TPR) before and after renal wrapping on day 0 in two rabbits. In one rabbit there was a significant early rise in CO, whereas in the other there was no change. Despite the different CO changes both developed closely similar rises in MAP and TPR. C = control days.

LATE CHANGES

CO decreased progressively in renal wrap rabbits from a level of 99% of control on day 8 to 75% of control on day 32 (SED ± 5.5%; P < 0.01) (Figs. 3 and 4). The corresponding changes over the same period in sham-operated rabbits were small and not significant, CO falling from 101% to 95% (SED ± 3.7%). We also examined the CO changes per unit of body weight in view of the relatively greater weight loss in wrap rabbits as compared to sham-operated rabbits (see below). The differences between renal wrap and sham-operated rabbits were less pronounced when expressed in this manner, although they still were statistically significant. In both groups there was a progressive decline in CO per kilogram from postoperative day 8 onwards, which averaged 6.8 ± 0.65% of initial control per week in the wrap rabbits compared to 2.7 ± 0.32% of initial control per week in sham-operated rabbits (P < 0.01). By day 32, CO per kilogram was 79% of control in the wrap group, compared to 91% in sham-operated rabbits.

Over the same time period (days 8–32) MAP in the renal wrap rabbits rose from 110% to 155% of control (P < 0.001) whereas in the sham-operated group the rise was from 100% to only 108% of control (P < 0.01) (Figs. 3 and 4). TPR in the rabbits with renal hypertension rose from 112% (day 8) to 194% (day 32), with the corresponding change in the sham-operated group (from 99% to 118% of control) significantly smaller (Figs. 3 and 4). The changes in heart rate with time were small in each group and did not differ significantly. Stroke volume tended to be somewhat lower in the wrap group as compared to sham-operated rabbits, but the difference was significant only on day 32 (−16.9 ± 3.9%; P < 0.001).

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BODY WEIGHT (SERIES B)

The changes in body weight after wrapping differed from those observed after sham operation. In the wrap rabbits there was no significant change in body weight until day 16, but after that there was a small weight loss. On day 32 the body weight was 0.180 ± 0.067 kg below control (P < 0.05). In contrast, in the sham-operated group there was a small but progressive increase in body weight from day 8 after operation. By day 32 the rabbits were, on the average, 0.12 ± 0.017 kg above control (P < 0.01). The difference in entire 8-day period was 8.6 ± 1.4% of control. This was accounted for entirely by the difference in TPR over this period between the groups, which averaged 8.0 ± 2.5%. The changes in MAP, TPR, and heart rate on days 4 and 8 were similar in series B (Figs. 3 and 4) to those of series A.

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weight changes between groups was statistically significant (difference = 0.30 ± 0.07 kg; P < 0.001).

Discussion

In the present study the changes in CO during the 1st week after operation were virtually identical in the renal wrap and sham-operated rabbits. In each group the average CO became maximal on day 4 after operation. There was considerable variation in the responses of individual rabbits, but the proportions showing a particular change were similar in each group. Our findings suggest that in the rabbit the CO changes during the 1st week are a non-specific consequence of the preceding wrap or sham operation and did not influence the subsequent rise in blood pressure. In the rabbit during the 4th and 5th weeks after renal wrapping the rise in MAP was clearly due to a large rise in TPR, in agreement with results obtained for perinephritic and renovascular hypertension in other species. However, with the experimental design used in our present study the MAP and TPR of the renal wrap rabbits exceeded corresponding values of these variables in the sham-operated group by small but significant amount through the 1st week after operation. This suggests that this type of renal hypertension in the rabbit is "resistance-mediated" from the earliest stages.

The reduction in CO observed in the renal wrap rabbits during the 4th and 5th weeks has not been observed in chronic renal hypertension in the dog or rat. However, we have observed a similar reduction in iliac blood flow in rabbits with bilateral renal wrap hypertension. In these rabbits blood flow remained lower than in sham-operated rabbits after extensive block of all the autonomic effectors, suggesting that it was not mediated through the autonomic nervous system and not due to increased sympathetic constrictor activity, e.g., secondary to cardiac failure. The differences between wrap and sham groups were somewhat reduced but were still significant when CO was expressed per unit of body weight. It seems possible that some diminution in tissue vascularity related to the loss of tissue mass in the hypertensive rabbits may have partly contributed to the fall in CO. Our rabbits showed no overt signs of cardiac failure; right atrial pressures were not determined in the present study, but in a previous study from our laboratory right atrial pressures were not determined in the present study, the surgery involved in both renal wrapping and sham operation was relatively minor and the duration and depth of anesthesia were, as far as possible, the same. The close similarity in proportions of early CO responses after wrapping and sham operation is consistent with similar sequelae from the operation in each group.

The present findings for the rabbit do not support the view that increased cardiac output eliciting a generalized autoregulation of tissue blood flow is an essential step preceding the rise in TPR during the development of hypertension. Ledingham and colleagues postulated that a rise in blood pressure early in hypertension mediated through a rise in CO might trigger a myogenic constrictor response in the resistance vessels that produced a gradual rise in TPR and restoration of CO. However, no elevation in CO was observed in the study of Olmsted and Page and of Conway. Moreover, in the study by Ledingham and Pelling of one-kidney renal hypertension in the rat there was an immediate fall in CO followed by a small rise of about 10% above the level of the sham-operated group, with the difference in CO between groups maintained constant for the 4-week duration of the study despite rises in MAP and TPR. Lack of any return in CO toward control is contrary to the prediction of the autoregulation theory.

Strongest support for the autoregulation theory has come from experiments involving salt and fluid overloading in animals and man with markedly impaired or absent renal function. Similarly the studies of Bianchi et al. and Ferrario on one-kidney Goldblatt clamp hypertension and of Ferrario et al. on one-kidney perinephritic hypertension in dogs have reported rises in CO before TPR increased. Their data generally has been considered to provide support for the autoregulation theory. Bianchi et al. and Ferrario tightened a previously applied Goldblatt clamp without surgery, thereby avoiding the problem of surgical trauma. Their studies did not include a "sham-treated" (or untreated) control group to evaluate any non-specific time-dependent circulatory changes. However, all hemodynamic changes were related to the initial control values in each dog obtained under stable conditions over several weeks before tightening the clamp.

It is of interest that when our postoperative results are related to initial control they also can be interpreted as providing support for the autoregulation theory. For example, in our renal wrap rabbits of series A the average values of MAP and CO on days 4 and 8 were 108% and 109% of their own controls, respectively, i.e., consistent with the interpretation that the early rise in MAP is entirely due to a rise in CO. Although this hemodynamic relationship is true, it does not necessarily indicate that the rise in CO and MAP are causally related. To assess the specificity of the rise in CO in relation to the development of hypertension in our study we have compared the renal wrap group with the sham-operated group. Such a comparison provides what seems a more reasonable interpretation of our data—that the CO rises nonspecifically following the operative procedures in renal wrap and sham-operated groups, whereas the differences in TPR between the two groups can be accounted for by differences in TPR throughout the ob-
HEMODYNAMIC CHANGES IN HYPERTENSION/Fleisher et al. 639


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