Chronic Carotid Sinus Compression in Dogs: A Study of Hemodynamic Changes with and without Sinus Denervation

By J. Maxwell Little, Ph.D., A. Robert Cordell, M.D., and Eugene A. Conrad, Ph.D.

Wakerlin and his associates have reported\(^1\)\(^2\) that chronic bilateral carotid sinus compression in dogs resulted in a sustained elevation of the mean arterial pressure. This finding was confirmed by Hawthorne and Gaspar,\(^3\) who reported also that the elevated mean arterial pressure after bilateral carotid sinus compression was ameliorated by hypophysectomy. Kezdi\(^4\) reported that bilateral constriction of the external and internal carotid arteries did not result in an elevation of mean arterial pressure in the dog; subsequent section of the carotid sinus nerves bilaterally did result in a sustained elevation of mean arterial pressure.

After the report of Wakerlin et al., we became interested in this type of hypertension, for we wanted to study the effect of experimental hypertension of nonrenal genesis on several variables of renal function. A preliminary report\(^6\) of some of our findings concerning the hemodynamic effects of carotid sinus compression has been made. Here we will report more extensively on our observations of the effects of chronic partial compression of the carotid sinuses on the arterial blood pressure and heart rate.

Methods

Two groups of mongrel female dogs, weighing 10 to 12 Kg., have been studied. Group A consisted of three dogs, trained to lie quietly with loose restraining thongs. After a control period of blood pressure measurements, covering a period of 16 to 71 days with 4 to 8 measurements per dog on different days, the clamps were applied to both carotid sinuses.\(^*\) Under pentobarbital sodium anesthesia, the carotid sinuses were exposed bilaterally. The vessels adjacent to the sinuses were cleaned by dissection as thoroughly as possible and the area was denervated. The completeness of denervation was not checked by carotid occlusion. Clamps were selected so that there was obvious compression of the sinus without occlusion. The occipital artery was included in the same channel as the external carotid artery.

Beginning 2 to 3 days postoperatively, measurements of systolic pressure and diastolic pressure were made in the unanesthetized dogs by puncture of the femoral artery or one of its branches. The pressures were recorded from a Statham pressure transducer model P 23A with a Brush amplifier and recorder. A period of 15 minutes elapsed between restraining the dog and arterial puncture, and 5 minutes elapsed between arterial puncture and the beginning of the recording. The same observer made all measurements. From the pressure records, the average or mean arterial pressure, pulse pressure and heart rate were calculated. Separate measurements, 22 to 26 per dog in number, were continued for 422 to 485 days.

Group B consisted of five mongrel female animals. The dogs in this series were prepared and the measurements were made as in group A, except that every effort was made to retain the integrity of the innervation of both carotid sinuses at the time of clamp application. However, no attempt was made to test the integrity of the innervation by common carotid occlusion at the time of operation. The carotids were compressed after 12 to 38 control measurements per dog covering a period of 230 to 388 days. The first study consisted of 15 to 21 post-compression measurements, which were made over a period of 273 to 384 days.

The second study was concerned with the effect of increased sodium chloride intake. Following the period of post-compression measurements, the dogs were given 6 Gm. per day of sodium chloride in addition to the unknown amount in their diet. The salt was administered twice daily as either

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\(^*\)The clamps were kindly supplied by Dr. Wakerlin.
3 Gm. enteric-coated or non-coated tablets, or as 300 ml. of 1.0 per cent solution by stomach tube. The animals were observed for at least 15 minutes after each administration. Only occasionally was there evidence that the salt was lost by vomiting. From 9 to 13 observations per dog were made with sodium chloride administration, covering a period of 107 to 123 days.

The third study was concerned with the duration of the effects of chronic carotid compression. After the additional sodium chloride administration was stopped, the observations were continued for a period of 178 to 206 days, during which time 13 to 19 measurements per dog were made. The total number of days of observation after the clamps were applied for each dog varied between 593 and 695 days.

When the observations had been completed the dogs were anesthetized and the common carotid arteries and carotid sinuses were exposed. The patency of the arteries in the clamps was tested by probing and examination. In four of the dogs, the carotid sinus reflex was tested before removal of the clamp. One dog died from the pentobarbital sodium administration.

Results

The time course of measurements of systolic, diastolic, and pulse pressure for one dog in group A is given in figure 1. There was considerable variation in the pressure measurements, but in general there was an elevation of the averages for all three pressures, indicated by the dotted lines, after carotid sinus compression.

The same measurements for one dog in group B will be found in figure 2. There were rather large day-to-day variations in systolic pressure, and to a lesser extent in diastolic pressure, in the group B dogs. Therefore the variations in pulse pressure were also rather large. A precipitous fall in pulse pressure occurred 10 to 17 days after the carotid compression. In dog 109 there was a gradual decrease in pulse pressure, reaching a low plateau on the eighty-third day. In the other dogs, the decreases in pulse pressure were similar to that seen in dog 111 (fig. 2). The post-clamp intervals during which the precipitous decrease in pulse pressure occurred were: dog 110, 30 to 55 days; dog 112, 10 to 35 days; and dog 113, 15 to 50 days. The time interval may have been shorter in some of these dogs, but measurements were not made to determine this.

A comparison of the average control measurements and derived values with the average values obtained after bilateral carotid sinus compression for each dog in group A will be found in figures 3 through 6. The averages ± 2 standard errors are plotted for both control and post-clamp situations. The probability of the change in mean values for each dog is given. There were significant increases in systolic, mean, and pulse pressures.
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A comparison of the individual changes in average systolic and diastolic pressures for both group A and group B dogs. The probabilities of the individual changes in averages are given.

for all three dogs, and in addition there were significant increases in diastolic pressures and heart rates for dogs 107 and 108. The diastolic pressure and heart rate increased for dog 103, but the changes were not significant \((P > 0.2)\). The increases in blood pressure and heart rate were modest. The average increases were: systolic pressure +30, diastolic pressure +13, mean arterial pressure +21, and pulse pressure +17 mm Hg, and for heart rate +27 beats per minute.

The same values for the group B dogs will be found in figures 3 through 6 and table 1. The average control values and the average values obtained in the first post-clamp period are given for each dog. The systolic pressure increased in dog 112 \((P < 0.05)\) while it decreased in the remaining dogs, of which one increase (dog 109) was significant \((P < 0.001)\). The diastolic pressure increased significantly \((P < 0.01)\) in all dogs but one (dog 109). The mean arterial pressure decreased significantly \((P < 0.001)\) in dog 109 and increased significantly \((P < 0.001)\) in dog 112; otherwise the changes were slight. The pulse pressures decreased significantly \((P < 0.001)\) in all dogs. The heart rates increased significantly \((P < 0.05)\) in two dogs (109 and 112). The average increase in diastolic pressure in the four dogs showing a change was 20 mm Hg. The average decrease in pulse pressure for all dogs was 26 mm Hg.

The effects of sodium chloride administration are given in table 1 and summarized in figures 7 and 8. Comparing these values with those obtained before sodium chloride administration, but after carotid compression, one finds that in dog 109 there was a significant \((P < 0.01)\) increase in systolic and in mean arterial pressure \((P < 0.001)\), which restored the mean arterial pressure to the control level. For the first time there was a significant \((P < 0.01)\) increase in diastolic pressure for dog 109. There was a significant decrease in dog 111 of diastolic pressure \((P < 0.02)\) and a significant increase in pulse pressure \((P < 0.05)\), but the pulse pressure was still well below the control value. Dog 113 also showed a significant \((P < 0.05)\) increase in systolic pressure. The most interesting effect of sodium chloride administration is the tendency for a decrease in heart rate: three dogs, 109 \((P < 0.05)\), 111 \((P < 0.001)\) and 112 \((P < 0.05)\), showed significant decreases.

The effect of duration of carotid compression on the measurements is given in table 1 and summarized in figures 7 and 8. A comparison of the post-sodium chloride values with the pre-sodium chloride values reveals very slight changes. Two changes are of particular interest: the maintained elevation in
## Table 1

Effects of Sodium Chloride Ingestion and Time on Dogs with Carotid Sinus Compression (Group B Dogs)

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>Control (A)</th>
<th>After compression (B)</th>
<th>After compression-NaCl ingestion (C)</th>
<th>After compression-post NaCl ingestion (D)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. observ.</td>
<td>Days</td>
<td>Mean</td>
<td>S.E.</td>
</tr>
<tr>
<td>109</td>
<td>38</td>
<td>388</td>
<td>201</td>
<td>2.4</td>
</tr>
<tr>
<td>110</td>
<td>36</td>
<td>373</td>
<td>176</td>
<td>2.6</td>
</tr>
<tr>
<td>111</td>
<td>30</td>
<td>380</td>
<td>187</td>
<td>2.8</td>
</tr>
<tr>
<td>112</td>
<td>28</td>
<td>398</td>
<td>191</td>
<td>2.5</td>
</tr>
<tr>
<td>113</td>
<td>12</td>
<td>230</td>
<td>171</td>
<td>4.2</td>
</tr>
</tbody>
</table>

### Systolic Arterial Pressure, mm Hg

- **Diastolic Arterial Pressure, mm Hg**
- **Average Arterial Pressure, mm Hg**
- **Pulse Pressure mm Hg**
- **Heart Rate, beats/min.**
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FIGURE 5
A comparison of the individual changes in averages of pulse pressures for both groups of dogs.

diastolic pressure and the further decrease in pulse pressure for dog 109. Another point of interest is the trend towards restoration of the heart rates, in four of the dogs, after removal of sodium chloride administration.

On concluding the series of measurements, the clamps were removed from the dogs under pentobarbital sodium anesthesia, and one or both carotid sinus reflexes were tested by common cartoid occlusion. In dog 109 there was a 50 mm. Hg increase in pressure from occluding the left common carotid and a 45 mm. Hg increase from the right. The bifurcations of the common carotids were intact and pulsation appeared normal. In dog 110, occlusion of the left carotid was not tried, but occlusion of the right carotid gave a 20 mm. Hg rise in pressure. In dog 111 there was a 25 mm. Hg rise in pressure on left carotid occlusion and a rise of 15 mm. Hg pressure on right carotid occlusion. In dog 112, the clamps were found to be located subcutaneously on both sides. The clamps contained necrotic carotid sinus tissue. Identification of the left carotid artery at the site of clamp application was uncertain, but the right carotid appeared intact with no evidence of a bifurcation. Clamping the common carotid artery had no effect on blood pressure.

Dog 113 died from the anesthetic before occlusion of the carotid arteries could be accomplished. However, the clamps were in place. In all dogs, excepting dog 112, the sinuses and vessels adjacent to the sinuses were patent.

Discussion

Some striking differences exist between the two groups of dogs. In all dogs of group A there were significant but moderate increases of systolic blood pressure resulting from the carotid compression, while in group B only one dog showed a significant small rise of systolic pressure. The same difference was found in the changes of mean arterial pressure. However, with one exception in each group, both groups showed a significant rise of diastolic pressure, and one dog (109) subsequently had a significant rise of diastolic pressure (see table 1). Perhaps the most evident difference between the two groups is in the pulse pressure measurements. In group A the pulse pressure increased significantly for all dogs, while in group B it decreased significantly for all dogs. In group B the change in pulse pressure did not appear immediately after compression; for example, in four of the dogs the decrease occurred between the second and eighth week after compression. The results obtained with group A dogs are in general agreement with those obtained by Thomas7 during stepwise section of the four buffer nerves, although the mag-

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FIGURE 7
A summary of changes in means of systolic and diastolic pressures and heart rate for group B dogs during the three types of studies. ○—○ dog 109, □—□ dog 110, △—△ dog 111, ●—● dog 112, ■—■ dog 113.

The magnitude of the increases in pressure and heart rate was not as great in our dogs as in hers. The only known difference between the two groups was denervation of the carotid sinuses in group A, with an attempt being made to preserve innervation in group B. Although the preservation of innervation in group B was not verified immediately after the clamps were applied, there is evidence that the innervation was intact, at least on one side, in three of the four dogs tested at the time of sacrifice. It is certain that denervation occurred in dog 112 sometime after compression, but from observation of the animal the clamps did not migrate to the subcutaneous site until some months after compression. Further evidence that dog 112 was not atypical of group B was the marked decrease in pulse pressure, as opposed to the increased pulse pressure in the group A dogs.

Kezdi\(^4\) has reported that constriction of the internal and external carotid arteries distal to the sinus did not result in a rise of mean arterial pressure, while subsequent denervation of the sinuses bilaterally did cause a rise in pressure. Although constriction of the arteries above the sinus would probably not have the same physiological effect as compression of the sinuses, our results with the group A dogs are in agreement with those of Kezdi. Also, our results reinforce his suggestion that the hypertension attributed\(^1,2,3\) to compression of the carotid sinus probably is due to disruption of the carotid sinus nerves. However, our results with the group B dogs indicate that chronic compression of innervated carotid sinuses does have sustained hemodynamic effects, as shown by the rise in diastolic pressure and decrease in pulse pressure.

Since there had been no appreciable increase of the mean arterial pressure in group B, the additional effect of an excess of sodium chloride administration was studied. The administration of sodium chloride to the dogs with carotid sinus compression (group B) did not produce any marked effects on the pressures measured. It is true that dog 109 did exhibit significant increases of systolic, diastolic, and mean arterial pressures during this time, but it would be difficult to attribute these increases to the sodium chloride administration, since the other dogs in the group did not exhibit similar changes. In fact, one dog (111) showed a small but significant decrease of diastolic pressure during this time. It is possible that the effects noted with dog 109 represent a delayed response to carotid sinus compression even though the length of delay is surprising. One point of interest is the trend toward a decreased heart rate during the sodium chloride administration, with three of the five dogs showing significant decreases. The conclusion that this is due to the salt administration is reinforced by the observation that the heart rate tended to return to the pre-salt administration level after the salt administration was stopped. Why the
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heart rate should be related to salt administration under these conditions is not clear. Other changes noted during the post-salt administration period are not remarkable. In general, the changes previously observed were maintained through this period.

In the absence of measurements of cardiac output and calculated values for peripheral resistance for the two series of dogs, we have used the Circulatory Index (PP x HR) as a qualitative indication of changes in cardiac output, and the mean arterial pressure to calculate relative peripheral resistance values in order to obtain a qualitative indication of changes in peripheral resistance. Our confidence in the use of these values for the purpose of indicating qualitative changes is increased by comparisons we have made on nine anesthetized normal dogs in which the cardiac output was measured twice with a lapse of 2 to 3 hours between measurements, and in which systolic, diastolic, and an integrated mean arterial pressure were recorded. The cardiac output was determined by the Fick principle, using pulmonary arterial blood for a mixed venous sample. The ratio between the per cent change in cardiac output and the per cent change in Circulatory Index between the two measurements on individual dogs was calculated. Also, the ratio between the calculated per cent change in peripheral resistance, by the two methods, was calculated. If qualitative changes were reflected equally by the two methods, the ratios should equal one in each case. In six dogs, the change in heart rate between the first and second measurements was ± 20 per cent. For these dogs, the mean of the ratios and standard error for cardiac output per cent changes was 1.08 ± 0.08, and the mean of the ratios for peripheral resistance per cent changes was 0.95 ± 0.06. When the per cent change in heart rate approached 50, the Circulatory Index and the peripheral resistance calculated from it did not reflect accurately qualitative changes in cardiac output and peripheral resistance. It appears that one can use with some confidence the Circulatory Index and relative peripheral resistance calculated from it, in individual dogs, as qualitative evidence of changes in cardiac output and total peripheral resistance in the same animal.

We have applied these calculations to the two groups of dogs, and the average values will be found in table 2. In group A, carotid compression in the denervated dogs resulted in a relative increase in cardiac output and a relative decrease in peripheral resistance. The increased cardiac output might be expected in carotid sinus denervation, on the basis of measurements made in acute experiments. However, in acute experiments the peripheral resistance is reported to increase even though the magnitude of increase may be less than the cardiac output change. The results reported here on cardiac output and peripheral resistance changes, even though the validity may be open to some question, suggest that with chronic denervation of the

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A summary of changes in means of average arterial and pulse pressure for group B dogs during the three types of studies. The legend is the same as in figure 7.
Table 2

<table>
<thead>
<tr>
<th>Group and Procedure</th>
<th>Circulatory Index (average)</th>
<th>Peripheral Resistance (average)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A: control</td>
<td>5.044</td>
<td>0.0255</td>
</tr>
<tr>
<td>Group A: after carotid compression</td>
<td>5.541</td>
<td>0.0172</td>
</tr>
<tr>
<td>Group B: control</td>
<td>11.404</td>
<td>0.0128</td>
</tr>
<tr>
<td>Group B: after carotid compression</td>
<td>8.139</td>
<td>0.0187</td>
</tr>
<tr>
<td>Group B: NaCl admin.</td>
<td>7.766</td>
<td>0.0197</td>
</tr>
<tr>
<td>Group B: NaCl admin.</td>
<td>7.272</td>
<td>0.0205</td>
</tr>
</tbody>
</table>

*Calculated from pulse pressure, heart rate and mean arterial pressure.

1 Circulatory index: PP X HR.

Peripheral resistance: \( \frac{MAP}{\text{Circulatory index}} \)

Carotid sinus the primary effect may be an increase in the cardiac output with other baroreceptors attempting to moderate the resulting rise in arterial pressure by decreasing the peripheral resistance.

The calculations for group B dogs (table 2) indicate that, with chronic compression of innervated carotid sinuses, there is a relative decrease in cardiac output and a relative increase in peripheral resistance. If one assumes that the clamps on an innervated sinus decrease the distensibility of the carotid sinus and increase the tension on the nerve endings, having an effect similar to the local application of vasoconstrictors, the influence of the clamp on hemodynamics would be the same as an increase in endosinus pressure, although the endosinus pressure is unchanged. The decrease in cardiac output might then be expected on the basis of acute experiments, but the increased peripheral resistance would not be expected. This same line of reasoning suggests that chronic compression of the innervated carotid sinus decreases the cardiac output primarily, with other baroreceptors attempting to maintain the arterial pressure through an increase in peripheral resistance.

Summary

In two groups of dogs the carotid sinuses were chronically compressed bilaterally by the application of plastic Wakefield clamps. In the first series of three dogs, the carotid sinus nerves were sectioned and the adjacent vessel walls thoroughly cleaned. Chronic carotid sinus compression resulted in an increase in arterial systolic pressure, diastolic pressure, average arterial pressure, pulse pressure, and heart rate over a period of 422 to 485 days.

In the second series of five dogs, in which the carotid sinus innervation was preserved, chronic carotid sinus compression resulted in a variable but slight change in arterial systolic pressure, a consistent increase in diastolic pressure, a variable but slight change in average arterial pressure—with only one dog showing a consistent significant increase, a consistent decrease in pulse pressure, and a variable effect on heart rate over a period of 593 to 695 days.

The daily administration of 6 Gm. of sodium chloride per day to the second series of dogs resulted in no appreciable changes in pressure. However, there was a tendency for the heart rate to decrease, with three dogs showing a significant decrease. When the salt administration was stopped, the heart rates returned to values near those observed prior to salt administration.

The results suggest that in the first series of dogs, with the carotid sinuses denervated chronically, there is an increase in cardiac output and a decrease in peripheral resistance. In the second series of dogs, with innervation of the sinuses intact and with chronic compression, the results suggest a decrease in cardiac output and an increase in peripheral resistance.

References


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Discussion

Dr. Hawthorne: I think it is very interesting that three people have come to the same conclusion. The fact that Dr. Little’s Circulatory Index suggests that carotid sinus area compression with denervation results in increased cardiac output is entirely consistent with our findings.

Dr. Mendowitz: How about without denervation?

Dr. Hawthorne: Our contention is that the hypertension produced in these animals is due to denervation of the sinus.

Dr. Sancetta: Why, Dr. Little, in control group A, was the Circulatory Index half the Circulatory Index in dogs in group B?

Dr. Little: I do not know, other than that in group A both pulse pressure and heart rate were lower than in the group B animals.

Dr. Sancetta: I assume your control data were obtained before any manipulation.

Dr. Little: That is correct. I cannot explain this observation except in relationship to the differences in heart rate and pulse pressure at the time of the control measurements. I have no explanation for these differences.

Dr. Peterson: Did you say the administered sodium chloride was retained in the group B animals? If so, how did you determine this?

Dr. Little: The animals did not regurgitate the tablets of sodium chloride nor the sodium chloride solution within a period of 15 to 30 minutes after they were administered. I did not mean to imply sodium retention in the usual sense.
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