The Acute Effects of Elimination of the Moderator Reflexes Upon Cardiac Output and Total Peripheral Resistance in the Anesthetized Dog

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The abrupt rise in mean arterial pressure resulting from elimination of the moderator reflexes is not accompanied by a significant increase in cardiac output. The acute hypertension is therefore attributed to a severe generalized vasoconstriction. The severity of this vasomotor response progressively diminishes during the interval immediately following denervation.

In a series of experiments recently completed in this laboratory, the pressoreceptor pathways were interrupted during determination of the relationships between pressure and flow in the systemic circulation. Immediately after denervation, the mean arterial pressure ascended steeply to attain a maximum value. The pressure then declined and stabilized ultimately at a hypertensive level. The total peripheral resistance determined at this plateau was consistently higher than the values observed just prior to denervation. This finding was not consonant with the studies of Charlier and Phillipot, who reported that the sharp rise in mean arterial pressure engendered by carotid occlusion or by moderator nerve section was accompanied by a proportionate augmentation of cardiac output. Therefore, no consistent alterations in calculated total peripheral resistance were observed in their studies.

The present investigation was undertaken to establish the temporal alterations in cardiac output and total peripheral resistance after abrogation of the moderator reflexes, and to attempt to reconcile the apparent discrepancies between these studies.

Methods

Nineteen experiments were completed successfully upon mongrel dogs weighing between 10.2 and 29.1 Kg. (mean, 19.3 ± 5.2). Three of these experiments were effected under chloralose anesthesia (100 mg. per kilogram intravenously), and two others under the regimen of morphine, dialurethane* and pentobarbital recommended by Foltz and his colleagues. All of the remaining studies were performed after an initial dose of morphine sulfate, 20 mg. subcutaneously, followed by sodium barbital, 200 mg. per kilogram body weight intravenously. Mean arterial pressure was registered continually by means of a damped mercury manometer. Cardiac output was estimated by the direct Fick technic. Oxygen consumption was measured with a Benedict-Roth spirometer connected to a tracheal cannula. Mixed venous blood samples were secured from the pulmonary artery through a no. 8 cardiac catheter. The position of the tip of the catheter was verified at autopsy. Duplicate determinations of the oxygen content of arterial and mixed venous samples were made by the method of Roughton and Scholander.

In each experiment, the bifurcation of the carotid artery was exposed bilaterally, and loose ligatures were placed about the arterial branches with as little disturbance as possible to the reflexogenic zones or the accompanying nerves. The vagosympathetic trunks were isolated in a similar manner at the mid-cervical level.

In twelve of these experiments, after all preliminary procedures had been accomplished, two pairs of arterial and venous blood samples were withdrawn three to five minutes apart for the estimation of two "control" cardiac outputs. The carotid sinus baroreceptors were then rapidly inactivated by ligating the common carotid artery and all of its branches by

* Dial-urethane supplied through the courtesy of Dr. A. J. Plummer, Ciba Pharmaceutical Products.
means of three heavy ligatures, which were so arranged that all connective and nervous tissues in the region were included in one of these three ties. That portion of the common carotid artery so isolated by means of these ligatures was then incised to expose any intact baroceptors to atmospheric pressure. Bilateral denervation of the sinus region was accomplished within two to four minutes by this procedure. Immediately afterward, the vago-sympathetic trunks were sectioned. Serial paired samples of arterial and mixed venous blood were withdrawn within two minutes after both denervation procedures had been completed, and at irregular intervals thereafter, depending upon the rate of change of the mean arterial pressure.

In seven other experiments a preliminary dose of heparin* was administered, and a pair of blood samples for the “control” cardiac output determinations were withdrawn. The baroceptor pathways were then interrupted in exactly the same manner and time sequence as previously described. However, in these experiments the mean arterial pressure was stabilized at the control level during and after the denervation procedure by connecting a large peripheral artery to a pressurized reservoir which had been adjusted previously to exactly the prevailing control pressure by means of a mercury escape-valve. In this manner, arterial pressure was not permitted to rise following denervation. Instead, a considerable portion of the blood volume was displaced into the large graduated cylinder which served as the pressurized blood reservoir. Serial blood samples were secured for the determination of cardiac output at time intervals which corresponded to those in the previous series of experiments.

The significance of the differences of the mean experimental values of pressure, cardiac output and resistance from their respective mean control values was evaluated by the t-test. The values of t, standard deviation (s), and probability (P) for each arbitrary interval of time are included at the bottom of each figure. The mean value during each interval is represented by a horizontal line.

RESULTS

When the baroceptor pathways were interrupted, the mean arterial pressure (MAP) rose precipitously, and attained a peak value usually within one minute. Figure 1 depicts the changes in arterial pressure observed in the twelve experiments in which no attempt was made to regulate the level of pressure. The average value during the control period was 108 ± 11 mm. Hg. During the first two minutes after denervation of the pressoreceptor zones, the mean value increased to 233 ± 23 mm. Hg. In the ensuing intervals, the arterial pressure declined very gradually in some experiments, more steeply in others, so that the average value 20 minutes or more after denervation was 172 ± 25 mm. Hg, a level still

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* Heparin supplied through the courtesy of Dr. W. R. Kirtley, The Lilly Research Laboratories.
Figure 2 illustrates the concurrent changes in cardiac output (CO) in this series of experiments. Each point in the “control” column represents the average of two independent determinations. In numerous instances, CO was measured more than once during certain of the arbitrarily chosen time intervals listed along the abscissa. In all such cases, these values were averaged and are represented by a single point in the chart. The mean CO during the control period was 3.41 ± 0.54 L per minute per square meter of body surface. After elimination of the moderator reflexes, CO increased to a variable extent in some experiments and decreased slightly in others. In only one experiment was an augmentation of CO as great as 70 per cent above control observed. It is obvious from figure 2 that a slight increase in the mean CO is manifest in each time interval after denervation, but the average outputs are not significantly different from the control value (P varies between 0.5 and 0.074). Certainly, the alterations in CO are negligible compared to the magnitude of the recorded changes in MAP.

The relative constancy of the CO coincident with the marked augmentation of MAP is reflected by an appreciable increase in the computed total peripheral resistance (TPR). As figure 3 demonstrates, the control TPR was 0.033 ± 0.008 PRU per square meter of body surface, where PRU is defined as mm. Hg per cubic centimeter per minute. In the first two-minute interval after denervation, the mean TPR increased to about twice the control level. In the subsequent time intervals, TPR progressively declined, attaining a mean value of 0.044 ± 0.011 PRU per square meter of body surface in the final period, a level which is still significantly greater than the control resistance (P = 0.02).

In figures 1, 2, and 3, open circles designate data from experiments performed under morphine-barbital anesthesia; closed circles, chloralose anesthesia; and closed squares, morphine-dial-urethane-pentobarbital anesthesia. From figure 3, it appears probable that a more appreciable increase in TPR is engendered by pressoreceptor denervation under chloralose or morphine-dial-urethane-pentobarbital anesthesia than under the morphine-barbital regimen.

A consistent increase in the erythrocyte concentration of the blood was observed in this group of experiments after abolition of the moderator reflexes, with a consequent enhancement of the oxygen carrying capacity of the blood. In table 1, the control values of arterial and venous oxygen content represent the average of two independent samples, while the data in the experimental columns are the mean values of five or six separate samples. It is evident from the table that the mean corpuscular concentration increased from a control value of 40.6 per cent to 46.9 per cent after denervation. The corresponding mean arterial oxygen content rose from 21.1 to 23.3 vol. per cent, while the venous oxygen content increased from 17.6 to 19.4 vol. per cent. The mean A-V oxygen difference, therefore, increased from 3.5 to 3.9 vol. per cent. The mean rate of oxygen utilization was augmented to a slightly greater extent (from 116.4 to 141.5 cc. per minute per square meter), accounting for...
MODERATOR REFLEXES AND TPR

Table 1.—Changes in Hematocrit Ratio, Arterial and Mixed Venous Oxygen Content, and Oxygen Consumption Resulting from Elimination of the Moderator Reflexes

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Control</th>
<th>After Denervation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hct. %</td>
<td>Arterial O₂ Content Vol. %</td>
</tr>
<tr>
<td>1</td>
<td>—</td>
<td>21.4</td>
</tr>
<tr>
<td>2</td>
<td>—</td>
<td>23.7</td>
</tr>
<tr>
<td>3</td>
<td>45.2</td>
<td>23.5</td>
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<td>4</td>
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<td>5</td>
<td>—</td>
<td>22.3</td>
</tr>
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<td>6</td>
<td>—</td>
<td>20.5</td>
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<td>7</td>
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<td>23.4</td>
</tr>
<tr>
<td>12</td>
<td>22.6</td>
<td>12.7</td>
</tr>
<tr>
<td>Mean</td>
<td>40.6</td>
<td>21.1</td>
</tr>
</tbody>
</table>

the slight, but not significant, rise in CO manifest in figure 2.

In the seven experiments where MAP was maintained at the control level by equilibration with a pressurized reservoir, denervation of the baroceptors resulted in the displacement of a large volume of blood into the reservoir, and a severe reduction in the minute output of the heart. Figure 4 shows that the mean control CO was 4.63 ± 0.79 L. per minute per square meter of body surface. Immediately after inactivation of the moderator reflexes, CO decreased precipitously. During the first nine minutes after denervation, the mean CO remained constant at 1.43 to 1.46 L. per minute per square meter of body surface, approximately one-third the control value. During the final two periods, the mean CO increased slightly to 1.78 and 1.91 L. per minute per square meter of body surface. Since MAP was maintained at the control level throughout each experiment, the changes in TPR are inversely proportional to the variations in CO illustrated in figure 4.

Blood began to enter the pressurized reservoir during the process of denervation and the displacement of blood was virtually completed within one minute after termination of this procedure. Although slight variations were observed in individual experiments, the average volume of blood displaced remained remarkably constant throughout the period of observation. In the first 9 minute interval, the mean volume was 682 ± 230 cc. This represents 3.6 per cent of the mean body weight for this series or approximately 40 per cent of the estimated blood volume. In the succeeding time interval, the mean value was essentially unchanged; namely 703 ± 236 cc.

Discussion

A wide diversity of opinions has been expressed concerning the effect of the moderator
reflexes upon the cardiac output. Riml[19] reported in 1929 that carotid occlusion resulted in an augmentation of CO in some experiments, a diminution in others, but that the response was characteristic for each animal. More recent work, however, indicated that carotid occlusion exerted a variable[11] or a negligible[12, 13] influence upon CO. Heymans and his colleagues[14] obtained contradictory results when they employed different methods for estimating CO. With the Fick technic, the CO varied inversely with the pressure exerted upon the isolated carotid sinus; by the cardiometric method, CO and intrasinusal pressure varied concordantly. Holt and his co-workers[15] reported a slight curtailment of CO compared to the relatively great diminution of MAP during sinus nerve stimulation. They postulated, nevertheless, that the reduction in CO was largely responsible for the hypotension which was elicited. Kenney, Neil, and Schweitzer, on the other hand, averred that neither stimulation of the sinus nerves nor perfusion of the isolated carotid sinuses at elevated pressures exerted a perceptible influence upon CO.

In a large series of experiments, Charlier and Phillipot[21] have observed a considerable and consistent increase in CO immediately after carotid occlusion or denervation of the baroreceptor zones. The rise of CO, on the average, was approximately proportionate to the augmentation of MAP. The hypertension, therefore, was attributed to the enhancement of CO. In approximately half of the experiments in which the presensorceptors were denervated, a secondary fall in MAP was observed after the maximum pressure was attained. This was ascribed to cardiac failure engendered by the severe hypertension, since it was accompanied by a proportionate reduction of CO.

The data accrued in the present series of experiments disagree in two cardinal respects to those published by Charlier and Phillipot: (a), elimination of the moderator reflexes was not attended by any consistent or significant alterations of CO, and (b), the secondary decline in MAP could not be imputed to cardiac failure. The data presented in this paper indicate that abolition of the moderator reflexes elicits a marked degree of generalized vasoconstriction, followed by a partial, progressive diminution of vasomotor tone. It has been emphasized by Green and his colleagues[7] that the assessment of vasomotor tone in isolated vascular beds is likely to be erroneous when based solely upon the computation of resistance. Moreover, it has been demonstrated that, in the systemic vascular bed deprived of the buffer reflexes, TPR may vary directly or inversely with MAP in individual experiments. Therefore, changes in vasomotor tone may be gauged with the greatest degree of certainty in experiments where (a), flow remains constant and variations in pressure are recorded, or (b), pressure is stable, and alterations in flow are detected. In the experiments depicted in figures 1 to 3, criterion (a) was satisfied, since MAP increased markedly while CO did not vary significantly. Cogent confirmatory evidence for vasoconstriction was adduced in the experiments illustrated in figure 4, where criterion (b) was fulfilled by virtue of a drastic reduction of CO, while MAP was maintained at a constant level.

In order to ascertain the reasons for the disparities between these results and those reported under similar circumstances by Charlier and Phillipot, the details of execution of the experiments must be compared. The studies of Charlier and Phillipot were effected under chloralose anesthesia, while most of the present experiments were conducted under morphine-barbital anesthesia. However, chloralose was employed in three experiments, and served only to exaggerate the apparent disparity. Figure 3 reveals that vasoconstriction was most pronounced in those animals which had received chloralose (solid circles). It is widely recognized that barbital markedly reduces the vagal inhibitory influence upon the sino-atrial node. Therefore, when this anesthetic is used, the control heart rate is very rapid, and the effects of the tachycardia normally evoked by buffer nerve section are attenuated. Therefore, two experiments were performed under a combination of morphine, diazepam, and pentobarbital to ensure a more nearly normal control heart rate. In these experiments, depicted by the solid squares in figures 1 to 3, the control cardiac frequencies were 72 and 98 beats per minute respectively. Shortly after denervation, these rates increased
234 and 158 beats per minutes respectively. Despite the magnitude of these changes, however, it is evident from figure 2 that CO was not elevated after moderator nerve interruption. McCubbin and Pageis have demonstrated that cardioacceleration plays only a minor role in the maintenance of the elevated pressure levels in chronic neurogenic hypertension.

In all of the experiments conducted by Charlier and Phillipot, as well as in those of the present series, CO was assessed by the direct Fick principle. The variables involved, however, were measured by slightly different technics. Since the changes in oxygen consumption are quite comparable, the differences in the methods used in its estimation may be eliminated from consideration.

The striking discrepancy in results resides in the denominator of the Fick equation; namely, the A-V oxygen difference. In the present study, a slight increase in the A-V difference was evoked as the result of denervation (table 1), while an appreciable reduction in this variable was reported by Charlier and Phillipot. In their experiments, mixed venous blood was obtained from the right atrium or right ventricle, while in the present series, samples were withdrawn from the pulmonary artery. Although it has been demonstrated that mixing is more complete in the pulmonary artery, an appreciable and quite consistent increase in the venous oxygen content was observed in both series after denervation. The major point of variance appears to be the arterial oxygen content. In our experiments, the arterial oxygen content increased to a slightly greater extent than did the venous, and this was accompanied by an appreciable augmentation of the hematocrit ratio. In the papers of Charlier and Phillipot, on the other hand, it is implied that the arterial oxygen content remained approximately constant after denervation, although the data are not presented. The reason for this discrepancy is obscure.

The mechanism responsible for the secondary drop in MAP after the initial peak also is debatable. In more protracted experiments, convincing pathological evidence indicates that congestive heart failure ultimately supervenes in the neurogenic hypertension due to abrogation of the moderator reflexes. In approximately half of their experiments, Charlier and Phillipot observed a decline in MAP immediately following the pressure summit. Since CO appeared to parallel this diminution in MAP, these investigators ascribed the acute fall in MAP to cardiac failure. In the present study, in each of the experiments represented in figure 1, a secondary decline in pressure was observed, although the rates of decline and the ultimate pressures attained were extremely variable in individual experiments. Figure 2 reveals, however, that no perceptible change in CO accompanied this MAP drop. By exclusion, therefore, vasodilatation of variable degree must supervene after the initial intense vasoconstriction (fig. 3).

The mechanism responsible for this secondary reduction in vasmotor tone has not been explained. It is certainly possible that baroreceptors exist which are not inactivated by the procedures which were employed. Aberrant afferent pathways from aortic pressoreceptors in the rat traverse the recurrent laryngeal nerve to join the vagus at the level of the superior laryngeal branch. If these fibers exist in the dog, they would not be interrupted by section of the vago-sympathetic trunk at the mid-cervical level. Therefore, in a few of the experiments included in figures 1 to 3, the recurrent laryngeal nerves were identified and transected. The results of these experiments are indistinguishable from those in which the recurrent laryngeal nerves remained intact. Heymans and his colleagues have described baroreceptors in the mesenteric vascular bed which ordinarily play no appreciable role in the regulation of MAP. They did postulate, however, that such a mechanism could account for the secondary decline in MAP which follows buffer nerve section. On the other hand, the reduction in vasmotor activity might originate within the medullary center itself. Cogent evidence has been proffered to indicate that parallel adjustments do take place in the cardiac accelerator center under analogous conditions.

**SUMMARY**

The changes in mean arterial pressure and cardiac output were assessed after abrogation of the moderator reflexes. The systemic blood
pressure ascended steeply to attain a maximum value within one minute after denervation. A secondary decline in pressure was then observed, which varied in rate and degree in individual experiments. Despite the pronounced variations in pressure, the cardiac output remained virtually constant throughout the entire experiment. Therefore, the initial hypertension was attributed solely to severe, generalized vasoconstriction, while the secondary pressure drop was ascribed to a subsequent relative diminution in vasomotor tone.

REFERENCES