Role of Venous Return in the Cardiovascular Response Following Injection of Ganglion-Blocking Agents

By JOSEPH H. TRAPOLD, PH.D.

With the technical assistance of Joan G. Sullivan, B.S. and James L. Hawkins, B.S.

The reduction of arterial pressure in anesthetized dogs following the injection of ganglion-blocking agents is dependent primarily upon a reduction in arterial vasomotor activity and secondarily upon a reduction in venous return associated with an increase in vascular capacity. When venous return is maintained at control levels, the administration of the blocking agents of this study invariably produce a decrease in total peripheral resistance (TPR). Ordinarily in the intact animal such a decrease in TPR is not observed due to a marked reduction in cardiac output which produces a secondary increase in TPR. The results of this study further suggests that the venous and arterial systems may differ in their sensitivity to the effects of ganglion-blocking agents.

The decrease in blood pressure produced by the injection of ganglion-blocking agents into man or laboratory animals is associated with an increased blood flow1–3 to and a decreased "vasomotor tone"4 in certain vascular areas. However, total peripheral resistance frequently does not change or may increase.1, 3, 4, 6 Grob and co-workers5 have reported that peripheral resistance decreased following the injection of hexamethonium in those patients whose cardiac output either did not change or increased and that total peripheral resistance either was unchanged or increased in patients whose cardiac output decreased. Similar findings have been reported by Moyer and associates.7 Recently, we have postulated4 that the changes in total peripheral resistance following the injection of ganglion-blocking agents depends upon the continued existence of a "critical closing pressure" in various vascular beds, and the degree to which venous return and subsequently cardiac output is reduced. On this basis the effect of ganglion-blocking agents upon total peripheral resistance depends on whether or not the reduced cardiac output and systemic blood pressure following their injection suffice to maintain the patency of peripheral blood vessels. The following study was designed to test this hypothesis.

METHODS

Twenty-six mongrel dogs of both sexes weighing 14 to 18 Kg., fasted at least 12 hours prior to each experiment, and anesthetized with barbital sodium, 250 mg./Kg., administered intravenously were employed in this study.

Experiments were conducted on open chest animals maintained under artificial respiration with the aid of a Palmer respiratory pump. Blood pressure was recorded with Hamilton manometers and blood flow with Shipley-Wilson rotameters. The experimental arrangement is illustrated in figure 1. Total venous return was measured and then returned via the azygos vein to the right atrium by means of a Maisch variable-control metering pump. The output of the pump, which was measured with a rotameter, was considered to represent cardiac output on the basis of the maxim that allowing sufficient time for the disappearance of transient events and stabilization of the system, the amount of blood ejected by the left ventricle must equal the amount entering the right ventricle. The initial delivery rate by the metering pump was adjusted in each experiment to maintain the mean arterial pressure at the precannulation level.

The reservoir and pump of the perfusion system were primed with 250 to 350 ml. of heparinized whole blood obtained from a donor dog. Clotting was prevented by the intravenous injection of 5 mg./Kg. of heparin sodium supplemented by 0.5 mg./Kg. of the anticoagulant every 20 min. As an additional precaution, the rotameters were rinsed with distilled water at the slightest indication of
any sticking on the part of the rotameter’s float. Base line checks were made as frequently as possible during the experiment and the system calibrated at the end of each experiment. Total peripheral resistance was calculated in PRU = mm. Hg × ml./min. of the pump output using blood pressure values obtained from the thoracic aorta.

Changes in arterial “vasomotor activity” were determined after the method suggested by Green and co-workers by comparing the plot relating aortic pressure to aortic flow over a flow range of 50 to 1100 ml./min during the control period, with a similar plot obtained in the experimental period.

Directional changes in vascular fluid capacity were estimated by maintaining the outflow of the flow system (fig. 1) constant and comparing the amount of blood in the reservoir before and after drug administration. Under these conditions a decrease in the level of blood in the reservoir was considered to indicate an increase in vascular fluid capacity.

The following ganglion-blocking agents were employed: chlorisondamine dimethochloride (Ecolid, Ciba), pentolinium tartrate (Ansolysen, Wyeth), and hexamethonium (Hexameton, Burroughs Wellcome). All drugs were diluted in distilled water and administered either via the azygos or a femoral vein. Doses were calculated as mg./Kg. of body weight.

Results

The effects of chlorisondamine and hexamethonium upon venous return, aortic blood pressure, and calculated total peripheral resistance in 6 dogs are presented in table 1. Those of the first 4 are typical of 9 of 11 experiments; the results of the last 2 are atypical. The measured caval blood flow will be referred to as “venous return” and flow from the metering pump as “pump output.” Frequently the terms pump output and cardiac output are used interchangeably.

Effect Upon Venous Return and Vascular Fluid Capacity. The injection of the ganglion-blocking agents chlorisondamine, pentolinium, and hexamethonium, into the azygos vein of anesthetized dogs was followed by a reduction in venous return within 3 min. after drug administration in 9 of the 11 experiments. When cardiac output via the metering pump was maintained at the control level following the injection of these agents, venous return gradually returned toward or to the predrug level. During these changes in venous return, the amount of blood in the reservoir diminished indicating an increase in the fluid capacity of the vascular system. Venous return and pump output usually reached a point of near equilibrium after the reservoir had been depleted of 200-250 ml. of blood. When the pump output was reduced to parallel the reduction in venous return, the level of blood in the reservoir was maintained and venous return eventually decreased to levels as low as 50 per cent or less of the predrug level; i.e., decreasing cardiac output to parallel the decrease in venous return led to a further reduction in venous return, thereby bringing about a vicious cycle in which ultimately the venous return and cardiac output were markedly reduced.

Role of Venous Return in Response of Arterial Pressure. The effect of the ganglion-blocking agents, chlorisondamine, pentolinium, and hexamethonium upon the aortic pressure of dogs whose cardiac output was maintained at the control level was compared with that of animals with uncontrolled cardiac output. As illustrated in figure 2, systolic and diastolic pressures were reduced by chlorisondamine (0.3 mg./Kg.) despite a constant cardiac output; however, the reduction was 33 per cent less than that observed in the control group. In order to produce a comparable reduction in the blood pressure of both groups, it was necessary to reduce the cardiac output of the constant venous return group to an average level of 340 ml./min. (fig. 3). Similar results were obtained following the injection of pentolinium and hexamethonium.

Effect Upon Pressure-Flow Relationship. As illustrated in figure 3, the intravenous injection
TABLE 1.—Effects of Ganglion-Blocking Agents on Venous Return, Aortic Pressure, and TPR of Anesthetized Dogs

<table>
<thead>
<tr>
<th>No. exp.*</th>
<th>Control period</th>
<th>Postdrug</th>
<th>Postdrug</th>
<th>Postdrug</th>
<th>Postdrug</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Venous return (ml./min.)</td>
<td>S</td>
<td>TPR</td>
<td>Venous return (ml./min.)</td>
<td>S</td>
</tr>
<tr>
<td>C7-16</td>
<td>885</td>
<td>855</td>
<td>0.089</td>
<td>777</td>
<td>833</td>
</tr>
<tr>
<td>C7-20</td>
<td>1110</td>
<td>1000</td>
<td>0.106</td>
<td>1080</td>
<td>1015</td>
</tr>
<tr>
<td>C7-30</td>
<td>953</td>
<td>840</td>
<td>0.121</td>
<td>755</td>
<td>867</td>
</tr>
<tr>
<td>H8-28</td>
<td>685</td>
<td>677</td>
<td>0.125</td>
<td>622</td>
<td>665</td>
</tr>
<tr>
<td>C7-24§</td>
<td>955</td>
<td>935</td>
<td>0.103</td>
<td>955</td>
<td>955</td>
</tr>
<tr>
<td>C7-25§</td>
<td>930</td>
<td>925</td>
<td>0.122</td>
<td>970</td>
<td>970</td>
</tr>
</tbody>
</table>

* C indicates that chlorisondamine [0.3 mg./Kg.] was injected; H indicates that 3 mg./Kg. of hexamethonium was injected.
† A. = Actual caval blood flow to pump; B. = Blood flow from pump to right heart via the azygos vein.
‡ Aortic systolic over diastolic pressure.
§ Two experiments in which venous return (caval flow) did not decrease following the injection of chlorisondamine. In experiment C7-24, the blocking agent was injected into the femoral vein whereas the injection of these agents was into the outflow tubing of the Maisch metering pump in all other experiments.

A shift in the pressure-flow curve indicates a decrease in “vasomotor activity.” Plotting the pressure-flow relationship during the periods of both decreasing and increasing flow results in the formation of a loop (fig. 3). Similarly, a loop is obtained in plotting the TPR-flow relationship. In both relationships (pressure-flow or TPR-flow), the portion of the loop obtained during the period of increasing flow is always shifted toward the flow axis as compared to the portion obtained during the period of decreasing flow. That the loop per se is not due to changes in neurogenic activity is suggested by its continued existence following the injection of ganglion-blocking agents.

Relationship of Venous Return to Total Peripheral Resistance (TPR). The injection of the ganglion-blocking agents used in this study produced a shift in the TPR-flow curve toward the flow axis (fig. 3). In addition, mechanically lowering cardiac output during the control period of each experiment produced a progres-
sive increase in TPR with a sharp increase in TPR occurring when the flow was reduced below 400 ml./min. Although the TPR-flow curve was shifted toward the flow axis following the injection of either chlorisondamine, pentolimium, or hexamethonium, mechanically lowering cardiac output still produced a progressive increase in TPR, but one starting from a lower value with a sharp increase occurring when the flow was reduced to 200 to 300 ml./min. When the pump output was maintained at the predrug level of blood flow following the injection of ganglion-blocking agents, the calculated TPR invariably decreased significantly from control values (table 1). On the other hand, when the pump output was decreased in an effort to bring it into equilibrium with the decrease in actual venous return following the injection of these agents, TPR increased toward the control value. In addition, an increase in TPR to or above the predrug value invariably occurred when the aortic pressure of these animals (controlled venous return group) was mechanically reduced to a level comparable to that level produced by the same agents in the control studies. These results are in agreement with those reported for the mesenteric bed of the anesthetized dog.

It is noteworthy that the TPR was significantly decreased by chlorisondamine in the 2 experiments (table 1) in which this agent failed to affect venous return.

**Heart Rate Changes Following Injection.** Although the injection of ganglion-blocking agents to the control animals always produced a slowing of the heart, they failed to alter the heart rate of the constant venous return animals. The heart rate of these latter animals was extremely constant throughout the entire experiment, failing to change even during the pronounced changes in cardiac output produced during the pressure-flow determinations. The only obvious differences between these 2 groups was that the latter animals were open-chest preparations.
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Discussion

The results of this study demonstrate that approximately 70 per cent of the reduction in arterial pressure produced by ganglion-blocking agents in dogs anesthetized with barbital sodium is dependent upon a reduction in vasomotor activity, the remainder of the pressure reduction being due to decreased venous return.

The cardiovascular response to ganglion-blocking agents differed in two respects between animals whose cardiac output was mechanically maintained at control values and those whose cardiac output was not maintained. First, the reduction in arterial pressure of the "maintained" animals was 70 per cent of the maximal reduction obtained in the "unmaintained" animals, and secondly, the calculated TPR of the arterial system of the maintained animals consistently and significantly decreased.

A role of venous return in the cardiovascular response to ganglion-blocking agents is indicated by the measured decrease in the venous return of all but 2 animals of this study following drug injection. The fact that this decrease in venous return occurred in the presence of a maintained cardiac output can be explained on the basis of an increased fluid capacity of the vascular system. This explanation is supported by the recovery of venous return toward or to the pre-injection level when the mechanically-maintained cardiac output was continued at the control level for 5 to 10 min. after drug injection. A similar recovery of venous return did not occur when the cardiac output was allowed to decline parallel with the initial decrease in venous return. Freis and co-workers have also reported an increase in the fluid capacity of the vascular system following the administration of ganglion-blocking agents to anesthetized dogs. It is probable that the extent of this increase in fluid capacity is the major factor in determining the degree of reduction in venous return produced by such agents. The possibility that the effects of ganglion-blocking agents upon the arterial and venous portions of the vascular system are separable is indicated by the absence of a decrease in venous return despite a significant reduction in arterial pressure following the administration of these agents to two animals.

The results of this study are consistent with and in support of our hypothesis, formerly noted, regarding the possible mechanisms involved in the changes in TPR which follow the administration of ganglion-blocking agents. In this respect, it has been demonstrated that the effect of these agents upon the arterial system per se invariably produces a decreased TPR which, however, may not be seen depending upon the degree of reduction in cardiac output. If the reduction in cardiac output is sufficient to reduce the mean arterial pressure below that necessary to maintain the patency of peripheral blood vessels (which we have arbitrarily chosen to refer to as critical closing pressure as defined by Burton), the TPR will tend to increase toward or above the control level. This concept receives particular support from the observed effect of ganglion-blocking agents on the TPR-flow (i.e., TPR-cardiac output) relationship curve. This consisted of a reduction in the TPR and a shift of the curve toward the flow axis. However, when the flow was mechanically reduced to values comparable with the reduced cardiac output produced by ganglion-blocking agents in previously reported studies, the TPR returned to or above the predrug value. In addition, as previously noted these studies have demonstrated that vasomotor activity is reduced following the administration of such agents. Therefore, these data are in agreement with the studies of Green and co-workers in which it was demonstrated that peripheral resistance may vary independently of changes in vasomotor activity. Thus, it is apparent that ganglion-blocking agents may produce a decrease in vasomotor activity and at the same time an increase in TPR depending upon the extent to which they reduce cardiac output. In light of this factor one can not state what influence these drugs may have on vasomotor or neurogenic arteriolar tone solely on the basis of changes in TPR when cardiac output is not controlled. The results of this study are not necessarily in contradiction to the results obtained by Smith and Hoobler in
hypertensive patients. However, our results do suggest that their conclusion that the effect of ganglion-blocking agents upon neurogenic arteriolar tone is minor may not be valid. The report of Grob and co-workers regarding the effect of hexamethonium in hypertensive patients confirms the important relationship between the effect of such agents on cardiac output and on TPR.

**SUMMARY**

The injection of the ganglion-blocking agents, chlorisondamine, pentolinium, and hexamethonium to barbital anesthetized dogs in which venous return to the right heart and thus cardiac output was maintained at control levels, invariably produced a decrease in aortic blood pressure and total peripheral resistance (TPR). At the same time a decrease in caval blood flow occurred in 9 of 11 dogs. The reduction in aortic pressure of the animals of this study was associated with a shift of the pressure-cardiac output curve toward the flow axis; i.e., reduced "vasomotor activity." In the intact animals of this study whose cardiac output was not controlled, the reduction in blood pressure produced by ganglion-blocking agents was dependent primarily (approximately 70 per cent) upon a reduction in arterial vasomotor activity and secondarily (approximately 30 per cent) upon a reduction in venous return. The changes in TPR which follow the injection of the above blocking agents have been shown to depend upon two factors, a reduction in arterial vasomotor activity which is consistently associated with a decrease in TPR unless the degree of reduction in venous return and, thus, cardiac output, is sufficient to lead to a decrease in blood pressure lower than the "critical closing pressure" of various vascular beds, in which event the TPR will return toward or rise above the control value. The results of this study strongly suggest that the susceptibility of the arterial portion of the cardiovascular system of "nonhypertensive" barbiturate anesthetized dogs to the effects of ganglion-blocking agents is separable from and greater than the susceptibility of the venous system to the effects of these agents.

**Summario in Interlingua**

Le injection del agentes ganglioblocante chlorisondamina, pentolinium, e hexamethonium in canes anesthesiate per barbital, in le quales le retorno venose al corde dextere—e assi etiam le rendimento cardiac—esseva mantenite a nivellos de controlo, invariabilemente produceva un reduction in le pression sanguinee aortic e in le total resistencia peripheric. Al mesme tempore in 9 del 11 canes occurreva un reduction in le fluxo del sanguine caval. Le reduction in le pression aortic del animales de iste studio esseva associate con un displacimento del curva de pression e rendimento cardiac verso le axe del fluxo, i.e., reduceite "activitate vasomotori." In le animales intacte de iste studio, in le quales le rendimento cardiac non esseva regulate, le reduction del pression sanguinee producite per agentes ganglioblocante dependeva primarimente (in approximativemente 70 pro cento del casos) de un reduction in le activitate vasomotori arterial e secundarimente (in approximativemente 30 pro cento) de un reduction in le retorno venose. Il esseva demonstrate que le cambiamentos in le total resistencia peripheric que sequ le injection del supra-mentionate agentes blocante depende de duo factores: le reduction in activitate vasomotori arterial que es normalmente associate con un reduction in le total resistencia peripheric, e le grado de reduction del retorno venose e assi del rendimento cardiac. Le grado de reduction del retorno venose e del rendimento cardiac pote esser sufficiente a producer un reduction de pression sanguinee usque a infra le "critic pression de clausura" de varie vasculaturas. In iste caso le total resistencia peripheric retorna verso le nivello de controlo o mesmo se eleva supra illo. Le resultatos de iste studio fortemente indica que in "nonhypertensive canes" anesthesiate per barbituratos, le susceptibilitate del portion del sistema cardiovascular al effectos de agentes ganglioblocante pote esser separate ab le susceptibilitate del sistema venose a iste mesme agentes e que le prime de istos es plus grande que le secunde.
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