Physiological Differences between the Effects of Neuronally Released and Bloodborne Norepinephrine on Beta Adrenergic Receptors in the Arterial Bed of the Dog

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ABSTRACT
This investigation was designed to define the role of the beta adrenergic receptors in the regulation of peripheral vascular resistance and to determine whether norepinephrine released from nerve terminals acts at the same receptor sites in the arterial bed as injected norepinephrine. In 34 anesthetized dogs the skinned hindlimb was perfused at a constant flow rate, and in 8 dogs a segment of the splanchnic vascular bed was similarly perfused through the aorta. The hemodynamic responses of the isolated perfused beds of control dogs were compared with those of dogs in which the alpha receptors had previously been blocked with phenoxybenzamine, thereby maximizing any contribution of the beta receptors. In the control animals, both carotid sinus hypotension and norepinephrine administered directly into the perfused segment increased vascular resistance. In those animals subjected to alpha-receptor blockade, carotid sinus hypotension still caused reflex vasoconstriction, though it was considerably attenuated, but intra-arterially injected norepinephrine produced vasodilation. Following subsequent beta-receptor blockade, no potentiation of reflex constriction occurred, although the response to injected norepinephrine reverted to constriction. These findings suggest that norepinephrine released from nerve terminals in the arterial tree does not produce physiologically significant beta-receptor stimulation; humorally transported norepinephrine, however, stimulates both alpha and beta receptors.

ADDITIONAL KEY WORDS
control of peripheral vascular resistance
propranolol isolated hindlimb
baroreceptor reflexes

It is somewhat paradoxical that norepinephrine, the adrenergic neural mediator, stimulates both alpha and beta adrenergic receptors, since these two types of receptors usually exert opposite effects. In the peripheral arterial bed, stimulation of alpha adrenergic receptors causes vasoconstriction, while stimulation of beta adrenergic receptors produces vasodilation (1). Although it is generally agreed that neuronally released norepinephrine produces vasoconstriction by stimulation of alpha adrenergic receptors, little information is available concerning the effects of neuronally released norepinephrine on beta receptors in the resistance vessels. Reviewing the literature, Green and Kepchar could find no evidence that the beta receptors located in the arterial tree are innervated (2). More recently, however, Folle and Aviado concluded that the vasodilation in the limbs observed during recovery from anoxemia results from neural stimulation of beta adrenergic recep-

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tors (3). The present study was designed primarily to attempt to define the physiological significance of the beta adrenergic receptors in the arterial tree. In addition, it has generally been assumed that norepinephrine acts at the same receptor sites, whether it is released from the adrenergic nerve endings by sympathetic stimulation or is transported to these sites through the blood stream. To study this problem, the effects of norepinephrine released reflexly as a result of carotid sinus hypotension were compared with the direct effects of intra-arterially administered norepinephrine.

**Methods**

Studies were carried out on 34 dogs, ranging in weight from 18.8 to 25.0 kg, in which the normally innervated hindlimb was perfused at a constant flow rate, and in which, therefore, changes in perfusion pressure reflected changes in vascular resistance of the limb. Eight animals served as controls; 18 were treated with the alpha-receptor blocking agent phenoxybenzamine, administered intravenously in a dose of 5 mg/kg 3 days, 1 day, and several hours preceding the study. When given in this fashion, this large total dose of 15 mg/kg of phenoxybenzamine resulted in maximal blockade of the alpha adrenergic receptors without producing an unreactive vascular bed. Attempts to block alpha adrenergic receptors by the slow, intra-arterial administration of phenoxybenzamine invariably produced an unreactive arterial bed. In 8 dogs the effects of acutely induced blockade of beta adrenergic receptors were studied; in 3 it was produced by the slow administration of propranolol, 2 mg/kg, into the perfusion system, and in 5 varying degrees of beta-receptor blockade were achieved by the stepwise administration of propranolol in doses ranging from 0.005 to a total of 0.315 mg/kg.

The animals were anesthetized with a combination of morphine (3 mg/kg sc), urethane (480 to 960 mg/kg iv), and chloralose (48 to 96 mg/kg iv). They were allowed to breathe spontaneously, and 100% O₂ was administered at a rate of 2 liters/min through a catheter inserted into the tracheal tube. Bilateral cervical vagotomy was performed to nullify the effects of stimulating the aortic arch baroreceptors. The paw was amputated in all 8 control dogs, in 16 of the 18 dogs treated with phenoxybenzamine, and in all 8 dogs treated with propranolol. The skin was removed from the hindlimb in 6 of the control dogs, in 9 of the animals in which the alpha receptors had been blocked, and in all 8 animals in which the beta receptors were blocked. These procedures were performed to insure that the blood flow was directed predominantly to the vascular bed of skeletal muscle. However, the results did not appear to be influenced by these maneuvers. The skinned limb was wrapped in towels that had been soaked in warm saline, and the temperature at the surface of the limb was measured with a thermistor. A second thermistor was inserted into the jugular vein to monitor the temperature in the trunk, and in all experiments the temperatures in the trunk and limb were maintained within the physiologic range.

The lower abdominal aorta, exposed through an abdominal incision, was cannulated, and blood was permitted to flow from the aorta into a large reservoir that had initially been primed with 1,000 ml of blood obtained from donor dogs and then thoroughly mixed with that of the experimental animals. From this reservoir it was pumped at a constant rate by a sigmamotor pump, via a heat exchanger, into the distal end of the external iliac artery. Blood flow from the pump was kept constant throughout each experiment, and the range in different experiments was from 61 to 160 ml/min. To eliminate possible collateral channels to the limb, the aorta was ligated above the trifurcation, as were the inferior mesenteric, the spermatic or ovarian, and deep circumflex iliac arteries, the middle sacral trunk, and all accessible lumbar arteries (4). Blood pressure in the limb was measured via a catheter inserted into the deep femoral artery; trunk pressure was recorded from the brachial artery. Intra-arterial injections were made just proximal to the pump, and the volume of the injectate was usually 0.2 ml. Injections of similar amounts of saline were made frequently to serve as controls; in the case of norepinephrine, control injections were also made using its preservative.

Dose-response curves to norepinephrine were obtained in each untreated dog. In 12 of the 18 animals treated with phenoxybenzamine the doses of norepinephrine administered as the free base to the hindlimb were the same as in the untreated dogs and ranged from 0.01 to 0.50 μg/kg total body weight; in 4 animals doses up to 2.0 μg/kg were used, and in the 2 remaining dogs the effects of 1 × 10⁻³ to 5 × 10⁻³ μg/kg were studied.

The direct effects of intra-arterial norepinephrine administration were compared with the effects of norepinephrine known to be released reflexly as a consequence of carotid sinus hypotension produced by carotid artery occlusion and

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by hemorrhagic hypotension. Both common carotid arteries were occluded for 45 to 60 sec and the greatest change in perfusion pressure that occurred during this time was measured. Mean arterial pressure in the trunk was maintained, by transfusion of blood, above 100 mm Hg in both the untreated dogs and in those subjected to blockade of alpha adrenergic receptors to insure that carotid occlusion produced an adequate stimulus. In the 8 dogs treated only with propranolol, only the effects of carotid occlusion were studied.

In 7 of the animals subjected to blockade of alpha adrenergic receptors, blockade of beta adrenergic receptors was subsequently produced by the slow administration of 2 mg/kg propranolol into the cannula perfusing the hindlimb. The effects of reflexly released and injected norepinephrine were then compared again.

In another series of 8 dogs, the spleen and both kidneys were removed, and the segment of the aorta extending from just cephalad to the superior mesenteric artery to just caudad to the inferior mesenteric artery was isolated and perfused at a constant rate. The reservoir system used in the hindlimb studies was also used in these experiments. Four of these animals served as untreated controls, and in the other 4 the alpha adrenergic receptors had previously been blocked with phenoxybenzamine, as described above. The dose of norepinephrine administered to the untreated animals was 0.5 µg/kg and 2.0 µg/kg was given to the dogs subjected to alpha-receptor blockade. Beta-receptor blockade was then induced in each of the 4 phenoxybenzamine-treated animals by the administration of 2 mg/kg propranolol into the arterial line of the perfusion system.

Results

ISOLATED HINDLIMB

The typical responses of an untreated control dog to carotid sinus hypotension are shown in Figure 1. The initial carotid occlusion produced considerable increases in the trunk pressure as well as the hindlimb perfusion pressure. To insure that the elevation in the limb perfusion pressure was not the result of the passive transmission of an evoked pressure rise in the trunk via open collateral channels, carotid occlusion was repeated, but by increasing the rate of blood loss from the aorta into the reservoir, the trunk pressure was not permitted to rise. Despite the stable trunk pressure, perfusion pressure increased to an extent similar to that observed during the first occlusion of the common carotid arteries. Also, when trunk pressure, and therefore carotid sinus pressure, was lowered by suddenly increasing the loss of blood from the aorta into the reservoir, a substantial elevation of perfusion pressure was once again observed. These tests of the adequacy of ligation of the collateral vessels were employed in all of the experimental studies.

Figure 2 demonstrates, for both the untreated dogs and those that had been given phenoxybenzamine, that when carotid sinus hypotension was produced, reflex vasoconstriction resulted, as manifested by an elevation of the hindlimb perfusion pressure. The mean perfusion pressure in the untreated animals rose from an average control value of 85 mm Hg to 146 mm Hg, signifying a marked increase in hindlimb vascular resistance. However, the elevation of perfusion pressure following carotid occlusion in the animals subjected to alpha-receptor blockade was attenuated significantly (P < .001), increasing from an average value of 74 mm Hg to 87 mm Hg, reflecting a smaller, but nonetheless significant increase (P < .001) in hindlimb vascular resistance. This difference in reflex vasoconstriction occurred even though the arterial blood pressure was similar in both groups of animals when the carotid arteries were occluded, the mean trunk pressure in the control dogs immediately before carotid occlusion averaging 123 mm Hg, while in the dogs treated with phenoxybenzamine it averaged 119 mm Hg.

The response of the perfused hindlimb to the injection of graded doses of norepinephrine is illustrated in Figure 3. In the untreated dogs, mean perfusion pressure at constant flow increased progressively, reflecting a dose-dependent increase in hindlimb vascular resistance. In contrast, in the animals subjected to alpha-receptor blockade, norepinephrine produced a fall in perfusion pressure, signifying a decrease in hindlimb vascular resistance.

Thus, in the dogs that had been treated with the alpha-receptor-blocking drug, norepinephrine released reflexly as a consequence of carotid occlusion still caused vasoconstric-
Typical responses of an untreated control dog to carotid occlusion (C.O.). Occlusion produced a reflex rise both in the trunk and hindlimb pressures. A similar increase in hindlimb perfusion pressure occurred during the second occlusion when trunk pressure was not permitted to rise by increasing the rate of aortic runoff. Perfusion pressure also increased to a comparable extent when reflex vasoconstriction was induced by sudden hemorrhagic hypotension. Paper speed, 0.25 mm/sec.

The results following blockade of beta adrenergic receptors in the entire group of dogs are depicted in Figures 3 and 5. In all animals that had been treated with phenoxybenzamine and were subsequently given propranolol, injected norepinephrine elevated perfusion pressure, in contrast to the decline produced by norepinephrine prior to the administration of propranolol (Fig. 3). In the untreated animals, neuronally released norepinephrine resulting from carotid occlusion produced an average increase of 71% in perfusion pressure, while in the animals treated with phenoxybenzamine, it raised perfusion pressure by an average of only 18% (Fig. 5). However, in contrast to the results observed with injected norepinephrine, the addition of pro-
Effects of carotid sinus hypotension produced by carotid occlusion on the mean hindlimb perfusion pressure. Open circles connected by broken lines represent the values of mean arterial pressure (BP) in the perfused hindlimb during the control period (left) and during carotid occlusion (right) in the untreated dogs; solid circles connected by solid lines illustrate the values observed in the animals previously treated with phenoxybenzamine. Horizontal lines on each side depict the average values for each group of dogs.

Prananolol did not augment the pressor response to carotid sinus hypotension; in the 7 dogs in which the effects of carotid occlusion were studied following both phenoxybenzamine and propranolol, the average increase in mean perfusion pressure of 18% was identical to that observed after phenoxybenzamine alone (Fig. 5). Furthermore, in the 8 dogs that did not receive phenoxybenzamine, but in which the effects of carotid occlusion were compared before and after treatment with propranolol, no potentiation of reflex vasoconstriction as a result of blockade of beta adrenergic receptors was observed. This lack of potentiation was noted at all dose levels of propranolol.

In the 2 dogs pretreated with phenoxybenzamine in which the effects of a broad range of norepinephrine dosage were studied, no detectable changes in hindlimb vascular resistance were seen at doses ranging from $1 \times 10^{-7}$ to $1 \times 10^{-4} \mu g/kg$. As the dose was increased, decreases in hindlimb perfusion pressure ensued and vasoconstriction never occurred. After treatment with propranolol, however, injected norepinephrine did produce an increase in perfusion pressure.

**Isolated Splanchnic Bed**

The results obtained when the splanchnic bed was perfused were comparable to those when the hindlimb was perfused, although the control values for perfusion pressure in all these animals were lower than in the isolated hindlimb preparation (Fig. 6). In the untreated control dogs, carotid sinus hypotension resulted in a reflex rise in perfusion pressure averaging 29%, while in the animals treated with the alpha-receptor-blocking drug, perfusion pressure rose by an average of 10% (Fig. 6A). The injection of norepinephrine, however, produced opposite results in the two groups of animals (Fig. 6B); in the untreated dogs it elevated perfusion pressure by an average of 71%, while in the animals treated with phenoxybenzamine it lowered perfusion pressure by an average of 16%. In the 4 animals treated with phenoxybenzamine, injected norepinephrine produced an elevation of perfusion pressure that averaged 14% after the addition of propranolol.

**Discussion**

The objectives of the present investigation were twofold: first, to define the physiologic role of the beta adrenergic receptors in the neural control of vascular resistance in the peripheral arterial bed and, second, to determine whether neuronally released norepinephrine acts upon the same population of receptors as intra-arterial norepinephrine. We elected to investigate the neuronal release of norepinephrine by producing carotid sinus hypotension, rather than by studying the release of norepinephrine induced by direct electrical stimulation of the lumbar sympa-
thetic chain for several reasons. Direct stimulation of the lumbar sympathetic chain in the dog activates sympathetic cholinergic fibers with consequent release of acetylcholine, a potent vasodilator substance (5). Such activation of the sympathetic cholinergic system has not been demonstrated as a result of carotid occlusion in dogs and, therefore, this system would not complicate the interpretation of our data. Also, reflex vasoconstriction resulting from carotid sinus hypotension is a physiologically important homeostatic mechanism, and we believed that it would be more significant to examine the effects of norepinephrine released by this mechanism rather than by the artificial stimulus of direct lumbar sympathetic trunk stimulation. Finally, we wanted the efferent sympathetic nerve traffic causing release of norepinephrine to arrive at the neuroeffector junction as physiologically as possible as regards the frequency, amplitude, and duration of the nervous impulses—variables that cannot be easily simulated by means of artificial stimulation.

It is appreciated that bilateral occlusion of the common carotid arteries, in addition to producing withdrawal of baroreceptor stimulation, may, by decreasing blood flow, also cause activation of the carotid body chemoreceptors and cerebral ischemia. All of these effects, however, would tend to augment sympathetic efferent outflow and thereby release norepinephrine at the neuroeffector junction, which was the desired outcome.

The basic plan consisted of comparing the responses of two perfused arterial beds to injected and reflexly released norepinephrine when all receptors were intact and following the administration, first of an alpha- and then of a beta-receptor-blocking agent. Since the

**FIGURE 3**
Changes in mean hindlimb perfusion pressure produced by intra-arterial administration of norepinephrine. In untreated dogs (open circles) norepinephrine caused a dose-dependent increase in perfusion pressure, while in the dogs treated with phenoxybenzamine (solid circles) it induced a fall in perfusion pressure. In those animals treated with phenoxybenzamine which were subsequently given propranolol (solid triangles), norepinephrine elevated perfusion pressure. Vertical bars = ± SEM. Isolated symbols represent data from single experiments.
RESULTS. The results were qualitatively identical in both the perfused hindlimb and the splanchnic vascular beds, they will be considered together.

In untreated animals, both the direct injection of norepinephrine into the perfused bed and norepinephrine released neuronally following carotid occlusion resulted in vasoconstriction, presumably as a consequence of predominantly activating alpha receptors. However, after producing complete blockade of the alpha adrenergic receptors as possible by administration of large doses of phenoxybenzamine, the injection of norepinephrine into the perfused bed now produced vasodilation, presumably as a consequence of unmasking the effects of unopposed beta adrenergic receptors (Figs. 3 and 4A). In contrast, this degree of alpha-receptor blockade did not result in a reversal of the response of the resistance vessels to carotid occlusion, which still produced a limited increase in the vascular resistance of the perfused limb (Figs. 2 and 4A). It is of interest that in one of the dogs subjected to alpha-receptor blockade,
administration of angiotensin, 1 μg/kg, caused a rise of 137 mm Hg in mean perfusion pressure, confirming that the vascular bed, itself, was still reactive despite treatment with phenoxybenzamine. These observations support the hypothesis that while injected norepinephrine stimulates both alpha and beta adrenergic receptors, neuronally released norepinephrine does not exert a significant effect on beta adrenergic receptors in the vascular bed. This hypothesis is strengthened by the obser-
vation of the disparate effects of propranolol on the response to neuronally released as opposed to injected norepinephrine. It would be expected that if norepinephrine concurrently stimulated both alpha- and beta-adrenergic receptors, the addition of beta-receptor blockade following almost complete alpha-receptor blockade would lead to the unopposed action of the remaining unblocked alpha receptors, thereby increasing the degree of vasoconstriction. Such augmentation of the constrictor response was, in fact, observed in the case of injected norepinephrine; in the dogs subjected to alpha-receptor blockade, propranolol caused a re-reversal of the dilating action of injected norepinephrine, which again exerted a vasoconstricting effect, although not as powerful as in the untreated animals. However, propranolol, administered either to normal dogs or to the animals that had been treated with phenoxybenzamine, did not augment the vasoconstrictor effects of neuronally released norepinephrine, a finding that again indicates that injected and neuronally released norepinephrine do not act upon identical receptor populations, and more specifically, that beta receptors are not activated, or are activated to only a minimal extent, by neuronally released norepinephrine.

Levin and Beck, also using an isolated perfused hindlimb preparation, have indicated that potentiation of the neural constrictor response occurs following beta-receptor blockade with propranolol (6). However, their data show considerable variability, with overlap between the values for the extent of vasoconstriction before and after the induction of beta-receptor blockade.

The possibility was considered that neuronally released norepinephrine does exert a significant action on beta receptors but that the phenoxybenzamine does not gain access to the alpha receptors at the neuroeffector junction and, therefore, that the degree of alpha-receptor blockade is insufficient to allow vasodilation following carotid occlusion. Such an explanation would account for the fact that phenoxybenzamine did not block the effect of carotid occlusion to the same extent as injected norepinephrine. If this were the case, however, the administration of propranolol should have augmented the reflexly induced vasoconstriction, since blockade of the beta receptors would have removed some of the opposing influence faced by the remaining unblocked alpha receptors. Since such augmentation was not observed, it appears more likely that the inability to produce vasodilation following carotid occlusion in the phenoxybenzamine-treated dogs is due to the sparsity or absence of beta receptors at the neuroeffector junction. In addition, as mentioned previously, the inability to potentiate reflex vasoconstriction in the normal dogs acutely treated with propranolol supports the belief that norepinephrine released from nerve endings does not reach areas with significant beta adrenergic responsiveness.

It might also be argued that the quantity of norepinephrine released at the nerve terminals by sympathetic nervous stimulation is much smaller than the quantity injected intra-arterially and that this small amount is insufficient to exceed the threshold of the beta adrenergic receptors. To investigate this possibility, very small doses of norepinephrine were injected into 2 dogs treated with phenoxybenzamine. While the lowest doses, 1 × 10^-7 to 1 × 10^-6 μg/kg, did not produce any effect, as the dose was increased, the first detectable effect was dilation. Furthermore, the dose of norepinephrine required to produce a pressor response comparable to that which resulted from carotid occlusion in the untreated dogs produced distinct vasodilation following phenoxybenzamine (Fig. 3). Therefore, it seems likely that the quantity of norepinephrine that was released neuronally would have been adequate to stimulate beta receptors in proximity to the neuroeffector junction if such receptors were present.

It should be emphasized that we do not believe that the present data indicate that activation of alpha receptors by bloodborne norepinephrine is more easily blocked than that induced neurally. Since neuronally released norepinephrine does not appear to have access to beta adrenergic receptors,
while injected norepinephrine exerts its effects by activating both alpha and beta receptors, it is apparent that the same degree of alpha-receptor blockade will seem to be more effective in inhibiting vasoconstriction due to injected norepinephrine because of the concurrent stimulation of beta receptors by it. In a recent paper, Levin and Beck assert that phenoxybenzamine reduced the vasoconstrictor response produced by stimulation of the lumbar sympathetic chain significantly more than the constrictor response produced by intra-arterially injected norepinephrine, that is, a preferential reduction in the neurogenic response occurred (6). By stimulating the lumbar sympathetic nerves directly, they were in all likelihood also activating the sympathetic cholinergic efferents. After partial alpha-receptor blockade produced by 0.5 mg/kg phenoxybenzamine, these dilator fibers would become proportionately more important and, therefore, an apparently greater attenuation of neurally induced vasoconstriction as compared to the vasoconstriction produced by injected norepinephrine would be expected. Unfortunately, these studies were not performed in atropinized dogs to eliminate the possible effects of released acetylcholine. Thus, the question of the relative ease with which neurally induced and vasoconstriction induced by injected norepinephrine can be blocked has not as yet been resolved.

In the present experiments, the effects produced by occlusion of the common carotid arteries could not have resulted from the release of catecholamines elsewhere in the body, for example, from the adrenal glands or the heart, since a large reservoir was interposed between the site of aortic runoff and the perfusion pump. Five to 10 min would have been required for such humoral agents to traverse this reservoir, and since the changes seen in the limb occurred within a few seconds following carotid occlusion, they were undoubtedly reflex in origin.

It is possible that the vasodilation produced by the injection of norepinephrine into dogs that had been subjected to alpha-receptor blockade may, in part, have been the result of a metabolic action of the catecholamine through the production of vasodilator metabolites. If this were the case, however, it would be anticipated that norepinephrine released from the nerve endings would have had a similar action.

The results of the present experiments do not explain the postanoxemic vasodilation which was prevented by beta-receptor blockade observed by Folle and Aviado (3). However, it is possible that their results may have been due to the release of epinephrine from the adrenal gland as a consequence of the hypoxic stimulus (7). That is, while vasoconstriction during the hypoxic period may have resulted from sympathetic nervous activity, when vasoconstriction was abolished by relief of the hypoxia, circulating epinephrine released from the adrenal glands during the hypoxic period could then have caused vasodilation as a result of its strong beta receptor-stimulating properties. This vasodilation could then be abolished by beta-receptor blockade.

Thus, the paradox that norepinephrine, the neural transmitter, activates receptors hav-
EFFECTS OF NOREPINEPHRINE ON BETA RECEPTORS

As illustrated diagrammatically in Figure 7, norepinephrine is capable of stimulating both alpha and beta adrenergic receptors in the peripheral arterial bed. However, neuronally released norepinephrine appears to exert a significant effect only on the alpha receptors while bloodborne norepinephrine reaches both alpha and beta receptors.

While the precise locus of the adrenergic receptors responding to injected and neuronally released norepinephrine cannot be completely defined, it would appear that at least a portion of the alpha-receptor effect of injected norepinephrine is exerted at alpha receptors located in the vicinity of the neuro-effector junction, since the effects of injected norepinephrine are markedly potentiated by cocaine, a drug that acts by preventing re-uptake of norepinephrine by the nerve terminals (8). It should be emphasized that the localization of receptor populations referred to in this paper represents a purely physiological localization and not an anatomical one, from the data presented here it is not possible to say whether the differential effect of neuronally released, as contrasted with bloodborne, norepinephrine occurs because they act at different sites within the same population of smooth muscle cells.

In summary, neural activation of the peripheral arterial bed might be considered to resemble that of the myocardium in that the neural transmitter, while capable of stimulating both types of receptors, actually activates only one type. However, unlike the myocardium, which contains only one class of adrenergic receptors, the arterial bed contains two, and while the neuronally released transmitter activates the alpha receptors predominantly or exclusively, norepinephrine and epinephrine released elsewhere in the body and transported to the receptors through the blood stream stimulates both alpha and beta receptors.

References

Demonstration that a rise in blood pressure in the carotid sinuses in the isolated head of dog B (per-
fused by donor dog A) cause a reflex fall in blood pressure and cardiac slowing in the trunk of dog B
connected to its head by only the vagus nerves.)
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