Cardiovascular Reflex Modulation of Plasma Catecholamine Concentrations in the Anesthetized Cat

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SUMMARY. The purpose of this study was to examine the role of the carotid sinus and cardiopulmonary mechanoreceptors in the reflex control of adrenal medullary catecholamine secretion. Afferent input from carotid sinus and cardiopulmonary mechanoreceptors was decreased by carotid occlusion or cervical vagal cold block, respectively. Increases in arterial pressure were significantly greater when either intervention was tested in the presence of the other, with the role of the carotid sinus baroreflex being dominant. Neither carotid occlusion nor vagal cold block resulted in a significant increase in plasma epinephrine or norepinephrine concentrations. However, carotid occlusion during vagal block caused a significant increase in plasma epinephrine (+87%) and norepinephrine concentrations (+128%). Likewise, vagal block during carotid occlusion increased plasma epinephrine (+62%) and norepinephrine concentrations (+73%). Similar experiments performed in a group of chemically sympathectomized animals (pre-treated with 50 mg/kg 6-hydroxydopamine) indicated that adrenal medullary norepinephrine as well as epinephrine release could be modulated by the carotid sinus and cardiopulmonary reflexes. Mean arterial blood pressure and heart rate were significantly lower in 6-hydroxydopamine-treated animals, compared with untreated controls. Although of lesser magnitude, responses to carotid occlusion and vagal block in 6-hydroxydopamine-treated animals were qualitatively similar to those in untreated animals. Plasma catecholamine concentrations did not increase from either manipulation. However, when the second manipulation was added to the first, significant increases occurred. We conclude from these data that both the carotid sinus and cardiopulmonary reflexes modulate the release of adrenal catecholamines. An interaction between the two reflexes exists whereby the influence of one reflex on catecholamine secretion is apparent only in the absence of the other input. (Circ Res 52: 391-399, 1982)

THE cardiovascular system maintains an adequate blood supply to all parts of the body under a wide variety of conditions and can alter regional blood flows to meet a wide range of demands. Neural reflexes play a significant role in immediate alterations of blood flow and modulate metabolic and humoral influences on the circulation.

Of the arterial baroreflexes, the carotid sinus reflex has been the most extensively studied, and the hemodynamic responses from this reflex mediated efferently through the sympathetic nerves are well documented. Data from some of the first studies (Bedford and Jackson, 1916; Heymans, 1929) demonstrated the importance of adrenal catecholamine secretion in response to hypotensive activation of the carotid sinus baroreflex. However, since that time, the role of adrenal catecholamines in the circulatory adjustments mediated by the carotid sinus baroreflex has been considered to be relatively minor. Korner et al. (1967) demonstrated that the hemodynamic responses to reflex activation of the arterial baroreceptors involved both neural and humoral components of the sympathoadrenal system. In more recent studies, Shimizu and Bishop (1980a, 1980b) implicated adrenal catecholamines in the effects of the carotid sinus reflex on systemic blood pressure and cardiac contractility in anesthetized cats.

Little information is available concerning the influence of cardiopulmonary reflexes on adrenal catecholamine secretion. In earlier studies, changes in adrenal catecholamine secretion mediated by the carotid sinus reflex were seen in vagotomized animals (Kaindl and von Euler, 1951; de Schaepdryver, 1959; and Critchley et al., 1973), but not in animals with intact vagi (Driver and Vogt, 1950; Kaindl and von Euler, 1951; and Hodge et al., 1969). This suggests that the vagi were exerting a tonic inhibition on the adrenal medulla. Since a significant involvement of cardiopulmonary reflexes in the control of other humoral systems has been reported (Jarecki et al., 1978; Thames et al., 1978; and Thames and Schmidt, 1979), it was postulated that changes in adrenal catecholamine secretion were involved in the reflex responses evoked by activation of receptors in the cardiopulmonary region.

In the present study, plasma catecholamine concentrations were measured during manipulations that altered the inhibitory input from the carotid sinus and cardiopulmonary reflexes in order to determine: (1) whether the carotid sinus and cardiopulmonary re-
flexes exert a tonic control over adrenal catecholamine secretion, and (2) whether an interaction exists between these two reflexes with respect to the control of adrenal catecholamine secretion.

Methods

Surgical Preparation and Experimental Protocol

Acute experiments were performed on 11 cats (1.6–4.2 kg) anesthetized by intraperitoneal (ip) injection of sodium pentobarbital (30 mg/kg). Unlike the majority of commonly used anesthetic agents, pentobarbital does not cause an increase in plasma catecholamine concentrations (Richardson et al., 1957; Callingham, 1975) and, therefore, pentobarbital was chosen as the anesthetic for this study. In addition, reflex control of the adrenal gland is mediated efficiently through the sympathetic nervous system and the inhibitory actions of barbiturates on cardiovascular reflexes are predominantly on parasympathetic, rather than sympathetic outflow, from the central nervous system (Pagani and McCubbin, 1965; Korner, 1971). Arterial pressure was measured in the aortic arch from a catheter inserted through the femoral artery. Mean arterial pressure (MAP) was obtained by electronic damping of the pulsatile pressure signal and heart rate (HR) was measured by use of a cardiotachometer coupler connected to the blood pressure recording.

A catheter was introduced retrograde through the left femoral vein to a level just above the adrenal vein for subsequent withdrawal of blood samples and the administration of fluid or drugs. The position of the catheter was confirmed at the end of the experiment. Body temperature of the animals was maintained by means of an electrical heating pad.

After a midcervical incision, both vagi and carotid arteries were dissected, and all branches of the common carotid arteries were tied and sectioned. The aortic nerves were identified and sectioned at their junctions with the superior laryngeal nerves, and the cervical sympathetic nerves were cut in the neck. In nine animals, the trachea was cannulated and artificial respiration was performed by a Harvard Apparatus Respirator. The volume and frequency of respiration were adjusted to suppress spontaneous respiratory movements and maintain blood gases and pH within normal limits. It was not possible to inhibit spontaneous respiration with the respirator in two animals; however, blood gases and pH remained within normal limits during the experiment without artificial respiration.

After the surgery, the animals were allowed to stabilize for 20–30 minutes before the experimental protocol was begun. Attenuation of carotid baroreceptor activity was produced by occluding both common carotid arteries (CO) with small clamps. Reversible bilateral vagal cold block (VB) was accomplished by placing the cervical vagi in a trough attached to U-shaped stainless steel tubing through which antifreeze precooled to −14°C was circulated. A previous study from this laboratory demonstrated that conduction of evoked responses over the cooled section were abolished when the temperature of the vagi reached 0–2°C (Shimizu et al., 1979).

Each animal was exposed to CO, VB, and the combination of the two interventions. Hemodynamic responses to the first intervention were allowed to stabilize before the second intervention was superimposed on the first. Blood samples (1 ml) were withdrawn from the femoral venous catheter immediately before each intervention and during the interventions after the hemodynamic responses had stabilized (approximately 1 minute during CO and 3 minutes during VB). After each withdrawal of blood, an equivalent volume of isotonic saline was immediately injected. After a set of interventions was performed, the animal was allowed to recover for at least 20 minutes, and another set of interventions was not performed until MAP and HR had returned to stable levels. Since it was anticipated that plasma catecholamine levels would increase with time, the order of the protocol was randomly assigned so that half of the cats received VB followed by CO first, and the other half received CO followed by VB first. In cases where a set of interventions was repeated in an animal, the hemodynamic data and plasma catecholamine concentrations were averaged, and only one value for each manipulation or combination of manipulations was used in the statistical analyses.

Treatment with 6-Hydroxydopamine

The primary source of plasma epinephrine (EPI) is the adrenal medulla. Circulating norepinephrine (NE), on the other hand, represents overflow from adrenergic nerve terminals as well as NE that has been released from the adrenal gland (Malmejac, 1964). Therefore, similar experiments were performed in a group of 6-hydroxydopamine (6-OHDA)-treated animals in order to determine whether adrenal medullary NE release could be modulated by the carotid sinus and cardiopulmonary reflexes. 6-Hydroxydopamine has been shown to destroy adrenergic nerve terminals effectively without destroying adrenal medullary catecholamine-containing cells or other nerves (Thoren and Tranzer, 1968; Prentice and Wood, 1975; Clark and Romanovsky, 1976).

Eleven cats were anesthetized with 30 mg/kg sodium pentobarbital (ip) and, under sterile conditions, a chronic femoral arterial and venous catheter were implanted and exteriorized at the dorsal midcervical region of the neck. Arterial blood pressure and heart rate were monitored and control responses to phrenaline hydrochloride (5 μg/kg, iv) and tyramine hydrochloride (0.1 mg/kg, iv) were obtained in the anesthetized state. On the day of the surgery and for the two following days, the animals received 11 mg/kg Liquamycin (im) to prevent infection. Three days after the surgery, 6-OHDA (50 mg/kg, iv) was administered to the conscious animals. Before 6-OHDA was given, post-junctional sympathetice blockade was accomplished by pretreatment with phentolamine hydrochloride (4 mg/kg, iv) and propranolol hydrochloride (1 mg/kg, iv). It has been shown that such pretreatment greatly attenuated the undesirable hemodynamic effects associated with the massive release of NE from adrenergic nerve terminals after 6-OHDA administration (Burks et al., 1975). While blood pressure and heart rate were monitored continuously, a total of 50 mg/kg 6-OHDA was administered. Responses to tyramine hydrochloride (0.1 mg/kg, iv) were determined in conscious animals. If the animals exhibited a pressor response to tyramine, an additional 20 mg/kg 6-OHDA was administered. Five days after the initial 6-OHDA treatment, acute experiments similar to those in untreated animals were performed to determine the effects of CO, VB, and the combination of the two.

Catecholamine Assay

Plasma epinephrine and norepinephrine were measured by the radioenzymatic method described by Peuler and Johnson (1977) with minor modifications. Catechol-O-methyltransferase (COMT) was partially purified from rat liver by the method of Axelrod and Tomchick (1958) adapted by Coyle and Henry (1973). Blood samples were withdrawn into chilled syringes containing a solution of
EGTA and reduced glutathione. After having been centrifuged in a refrigerated centrifuge to separate the blood, the plasma was removed and stored at −70°C. Endogenous catecholamines were converted to radiolabeled O-methyl catecholamine derivates by incubating plasma samples with COMT and the tritiated methyl group donor, S-adenosyl-L-methionine (SAM). The formed ³H-derivatives were then extracted and separated by thin layer chromatography. The zones containing ³H-metanephrine (epinephrine derivative), and ³H-normetanephrine (norepinephrine derivative) were scraped into separate scintillation vials and converted to ³H-vanillin by the addition of sodium periodate. After the addition of a toluene-based scintillation fluid, radioactivity was determined by scintillation counting.

Data Analysis

A one-way analysis of variance for repeated measures was employed in comparisons of the different interventions and combinations of interventions. Significant main effects were determined by the Student-Newman-Keuls multiple comparisons test (Sokal and Rohlf, 1969). Since it was only meaningful to compare the effects of the interventions to the control values obtained immediately before the interventions, the statistical analyses were performed in sets of three. For example, values for the control immediately before CO, CO, and CO + VB were compared separately from the control immediately before VB, VB, and VB + CO. To compare the changes between interventions that were not coupled in the experimental protocol, a separate data file of differences, rather than absolute values, was created and analyses performed. For example, by this method, comparisons between the changes due to VB and CO could be made. In order to meet the criteria for homogeneity of variance among treatments, a square root transformation was performed on the plasma catecholamine concentration data, and all statistical comparisons were performed on the transformed data (Wallenstein et al., 1980). When two groups of unpaired data were compared, Student's t-test was used. The criterion for significance was set at the 95% confidence level, P < 0.05.

Results

Effects of Carotid Occlusion and Vagal Cold Block

Hemodynamic Responses

An analog recording of blood pressure responses in a single cat during carotid occlusion and vagal cold block is shown in Figure 1. Carotid occlusion produced an increase in mean arterial pressure and the addition of VB produced a substantial further increase as shown in panel A of Figure 1. When the order of the interventions was reversed, as shown in panel B, VB alone produced a small increase in arterial pressure and subsequent CO during VB produced a pronounced further increase.

Figure 2 is a summary of the effects of carotid occlusion and vagal block on mean arterial pressure in 11 cats. Both CO and VB produced significant increases in arterial pressure, with the increase due to CO (36.4 ± 4.6 mm Hg) being greater than the increase due to VB (12.5 ± 3.9 mm Hg). When carotid occlusion was performed during vagal block (VB + CO), an enhanced response to CO occurred, with the increase in pressure due to CO (69.3 ± 5.2 mm Hg) being significantly greater than when CO was performed alone. Likewise, when vagal block was performed during carotid occlusion (CO + VB), an en-
hanced response to VB occurred, with the increase in pressure due to VB (33.7 ± 5.2 mm Hg) being significantly greater than when VB was performed alone.

Neither CO nor VB had a significant effect on heart rate. However, the combination of the two interventions resulted in a significant increase in heart rate. When carotid occlusion was performed first, followed by vagal cold block (CO + VB), heart rate rose from a control value of 209.9 ± 8.2 beats/min to 226.1 ± 6.8 beats/min. When the order of the interventions was reversed (VB + CO), heart rate rose from 214.7 ± 7.4 to 232.6 ± 7.2 beats/min.

Catecholamine Concentrations

A substantial variation in plasma EPI concentrations between different animals occurred, with control values ranging from 0.10 to 3.61 ng/ml. When CO was performed alone, plasma EPI concentrations did not change significantly, as shown in Figure 3. However, when carotid occlusion was performed during vagal block (CO + VB), plasma EPI concentrations increased significantly above the levels present during CO.

Similar to plasma EPI concentrations, there was a large variation in plasma NE concentrations between animals, with control plasma NE levels ranging from 0.43 to 3.65 ng/ml. Neither CO nor VB alone produced a significant increase in plasma NE concentrations (Fig. 3). However, when both procedures were combined, a significant increase occurred. Carotid occlusion during vagal block produced a significantly greater increase in plasma NE concentration than did CO alone. Likewise, vagal block during carotid occlusion produced a significantly greater increase in plasma NE concentrations than did VB alone.

6-Hydroxydopamine-Treated Animals

Test of Chemical Denervation

After 6-OHDA administration, all the animals exhibited general signs of sympathetic denervation such as miosis, relaxed nictitating membranes, and diarrhea. Responses to intravenous tyramine hydrochloride (0.1 mg/kg) and phenylephrine hydrochloride (5 μg/kg) were determined in anesthetized animals before 6-OHDA treatment and again 5 days after 6-OHDA had been administered. The increase in blood pressure produced by tyramine was significantly attenuated by 6-OHDA (64.0 ± 6.3 mm Hg before 6-OHDA vs. 10.3 ± 3.1 mm Hg after 6-OHDA). The reflex bradycardia caused by tyramine before 6-OHDA treatment (−87.4 ± 12.3 beats/min) was absent in the treated animals (−0.9 ± 2.0). When responses to phenylephrine after 6-OHDA treatment were compared to responses before 6-OHDA treatment, phenylephrine caused a greater increase in MAP (71.2 ± 5.7 vs. 35.8 ± 3.7 mm Hg) and less reflex bradycardia (−4.6 ± 2.4 vs. −66.8 ± 15.5 beats/min) after 6-OHDA treatment. The greatly reduced responsiveness to tyramine and the virtual abolition of reflex bradycardia during phenylephrine indicated that these animals were functionally denervated. The potentiated pressor response to phenylephrine after 6-OHDA can be explained by the lack of reflex bradycardia as well as postdenervation supersensitivity of vascular α-receptors.

In two animals, a bilateral adrenalectomy was performed at the end of the experiment. Mean arterial pressure fell from 73 to 50 mm Hg in one cat and from 85 to 45 mm Hg in the second cat. After adrenalectomy, no responses to carotid occlusion or vagal cold block were observed in either of these animals. These data indicate that the adrenal gland was important in the maintenance and reflex control of the circulation in chemically sympathectomized animals.

Hemodynamic Responses in 6-Hydroxydopamine-Treated Animals

Figure 4 is a summary of the effects of CO and VB on MAP in 11 6-OHDA-treated cats. CO produced a
significant increase in mean arterial pressure (32.4 ± 5.0 mm Hg). When vagal block was superimposed on carotid occlusion, a significant further increase was observed (24.5 ± 3.3 mm Hg). Similarly, a significant increase in MAP occurred during VB (15.2 ± 4.1 mm Hg), and the addition of CO resulted in a significant further increase in blood pressure (35.3 ± 5.2 mm Hg). The increase in MAP due to CO was significantly greater than the increase due to VB.

Mean control heart rate in this group of animals was 155.2 ± 7.3 beats/min, and the only significant change was an increase of 18.2 ± 3.5 beats/min due to carotid occlusion plus vagal block (CO + VB).

**Catecholamine Concentrations in 6-Hydroxydopamine-Treated Animals**

Plasma catecholamine concentrations in 6-OHDA-treated cats are expressed as percent of control ± SEM in Figure 5. Epinephrine concentrations were below the sensitivity of the radioenzymatic assay in two animals. Either due to difficulty in obtaining a blood sample or loss of sample due to problems encountered with the assay, it was not possible to obtain results for all six data points in each cat. Therefore, statistical comparisons were performed on results from eight animals in the series where CO was performed first and seven animals where VB was performed first. Control plasma EPI concentrations ranged from 0.03 to 0.44 ng/ml. Vagal cold block caused a significant increase in plasma EPI concentration to 256.3 ± 84.6% of control when performed during carotid occlusion (Fig. 5). Likewise, carotid occlusion during vagal block (VB + CO) resulted in a significant increase in plasma EPI concentrations (263.8 ± 104.7% of control). Plasma EPI concentrations significantly decreased (65.3 ± 13.2% of control) during CO alone.

Control plasma NE concentrations ranged from 0.14 to 4.52 ng/ml. Statistical comparisons were performed on results from 10 animals in the series where CO was performed first and nine animals where VB was performed first. Neither CO nor VB resulted in a significant increase in plasma NE concentrations (Fig. 5). However, in both cases in which the second manipulation was superimposed on the first (CO + VB and VB + CO), a significant increase above control plasma NE concentrations occurred (258.1 ± 58.5% of control).
control and 220.4 ± 71.3% of control, respectively). When vagal block was performed during carotid occlusion (CO + VB), plasma NE concentrations increased significantly above the concentrations present during CO.

Comparisons between 6-Hydroxydopamine-Treated Cats and Untreated Cats

Mean values ± SEM for control mean arterial pressure and heart rate in 11 6-OHDA-treated animals were 87.8 ± 3.3 mm Hg and 155.2 ± 7.3 beats/min, respectively. Both mean arterial pressure and heart rate were significantly lower than the corresponding values for 11 untreated animals (123.5 ± 2.6 mm Hg and 212.3 ± 7.4 beats/min). No significant difference was seen between the two groups in the changes in arterial pressure due to CO or VB. However, when both interventions were performed in concert, blood pressure rose significantly less in the 6-OHDA-treated animals than in untreated animals. When carotid occlusion was performed during vagal cold block (VB + CO), blood pressure rose 50.4 ± 6.0 mm Hg from control in 6-OHDA-treated animals as opposed to 81.8 ± 6.0 mm Hg in untreated animals. When the order of the interventions was reversed (CO + VB), blood pressure rose 56.9 ± 5.1 mm Hg in 6-OHDA-treated animals compared to 70.1 ± 4.6 mm Hg in untreated animals. No significant differences in plasma catecholamine concentrations were found between 6-OHDA-treated cats and untreated cats.

Discussion

The effects of carotid occlusion (CO) and vagal cold block (VB) on arterial pressure in this study are consistent with the concept that these manipulations result in a decrease in tonic inhibition of sympathetic efferent outflow from the central nervous system resulting in increased neurogenic tone to the vasculature (Guazzi et al., 1962; Oberg and White, 1970; Mancia et al., 1973; Shimizu et al., 1979). Other studies in the cat have demonstrated increases in arterial pressure during VB after muscarinic receptor blockade with atropine, suggesting that the hypertensive response to cervical VB is due to interruption of efferent traffic in the vago (Guazzi et al., 1962; Oberg and White, 1970; Shimizu et al., 1979). Since the major objective of the present study was to evaluate the reflex control of adrenal catecholamine secretion, atropine was not used. It has been shown that muscarinic as well as nicotinic cholinergic receptors are present in the adrenal medulla (Kayaalp and Neff, 1979) and that atropine is capable of blocking both chemically (Douglas and Poisner, 1965; Lee and Trendelenburg, 1967) and electrically (Feldberg et al., 1934; Lee and Trendelenburg, 1967) stimulated catecholamine release from the adrenal gland.

Since the vago were cooled in the neck, the exact location of the receptors mediating the pressor response during VB cannot be determined in these experiments. However, previous reports on a variety of experimental animals have shown that afferent fibers from the cardiopulmonary region are responsible for a tonic restraint on the circulation (Guazzi et al., 1962; Pillsbury et al., 1969; Oberg and White, 1970; Mancia and Donald, 1975; Shimizu et al., 1979). Sectioning of the vago below this region has no effect on the pressor responses to cervical vagotomy (Guazzi et al., 1962; Pillsbury et al., 1969; Mancia et al., 1973). The effects of cervical vagal cold block are eliminated after section of the cardiac nerves close to the heart in the cat (Oberg and White, 1970). Therefore, it seems likely that the effects of VB observed in the present study resulted from the blockade of afferent input from the cardiopulmonary region.

The aortic nerves were severed prior to the study, thus removing a source of neural inhibition that would no doubt have affected the responses to the two reflexes we studied. The following discussion is concerned with the interaction between the carotid sinus and cardiopulmonary reflexes in the absence of the aortic baroreceptors input.

Hemodynamic Responses

The pressor responses to CO were greater than those to VB, suggesting that the inhibitory influence of the cardiopulmonary receptors was less powerful than that of the carotid sinus baroreceptors, at least as long as the latter were allowed to exert their buffering effect. An enhanced pressor response to either CO or VB occurred when one intervention was performed in the presence of the other. This is in accord with the widely accepted interaction between inhibitory reflexes, such that the excitatory responses resulting from withdrawal of an inhibitory reflex are markedly enhanced when the inhibitory influences of other baroreceptor areas have been previously minimized (Heymans and Neil, 1958). The relationship between the two reflexes in the present study, both with regard to the dominance of the carotid sinus baroreflex and the enhancement of pressor responses by previous withdrawal of the other reflex, is in agreement with other studies in the cat (Oberg and White, 1970; Shimizu et al., 1980a).

The data from 6-OHDA-treated cats indicates that the carotid sinus and cardiopulmonary reflexes are functional in chemically sympathectomized animals and produce the same general hemodynamic responses as were seen in untreated animals.

The responses to tyramine and phenylephrine in 6-OHDA-treated animals suggested that they were sympathetically denervated. Therefore, it is difficult to explain the pressor responses to CO and VB in these animals, since plasma catecholamine concentrations did not increase significantly. However, it is worth noting that plasma NE concentrations increased in seven of 10 animals in response to either CO or VB. If the data from these seven animals is considered separately, the increases in NE were statistically significant. Ganther et al. (1974) demonstrated an increased responsiveness to exogenous NE in 6-OHDA-
treated dogs. Therefore, it is possible that increased vascular responsiveness to circulating catecholamines and residual amounts of locally released NE contributed to the pressor responses.

Plasma Catecholamine Concentrations

A large variation in baseline plasma catecholamine concentrations was seen between different animals in the present study. Approximately a 36-fold difference exists between the lowest and the highest plasma EPI concentration, and approximately a 7-fold variation exists in plasma NE concentrations. This is in agreement with studies in which a 10- to 30-fold difference in baseline plasma catecholamine concentrations between different animals has been reported (Kaindl and von Euler, 1951; Outshoorn, 1952; Woods et al., 1956; Bertler, 1958; Claviano et al., 1960; Vogt, 1965; Velasquez, 1979). Although it is impossible to determine the cause of this marked variability, differences in depth of anesthesia, degree of surgical stress, and exact location of the venous catheter all could be contributing factors in the present study.

Neither CO nor VB alone resulted in a significant increase in plasma catecholamine concentrations. However, when CO was performed in the absence of cardiopulmonary receptor input, i.e., during VB, a significant increase in plasma EPI and NE concentrations occurred. Conversely, when VB was performed after the carotid sinus baroreceptor input had been decreased by CO, plasma catecholamines increased significantly.

The possibility was considered that carotid sinus pressure was not maintained at a low enough level to see an effect on catecholamine secretion during CO. However, when CO was performed during VB, a significant increase in catecholamines due to CO occurred. Since the evoked hypertension when CO was performed during VB was greater than that seen when CO was performed alone, it appears that partial recovery of carotid sinus pressure during CO cannot fully explain the lack of increase in plasma catecholamines when CO was performed alone.

It appears that when the afferent input from one reflex is withdrawn, the remaining reflex prevents the release of adrenal catecholamines. This conclusion is supported by the fact that CO during VB produced a greater increase in plasma EPI and NE concentrations than did CO alone. Likewise, VB during CO produced a greater increase in plasma catecholamine concentrations than did VB alone.

The same pattern in plasma catecholamine concentrations was seen in 6-OHDA-treated animals. Vagal blockade alone did not produce a significant change in plasma EPI or NE concentrations. However, when VB was performed during CO, a significant increase in plasma catecholamine concentrations occurred due to VB. Carotid occlusion alone resulted in a significant decrease in plasma EPI concentrations, but the combination of VB plus CO resulted in a significant increase in plasma EPI concentrations. These data indicate that the inhibitory activity of the cardiopulmonary reflexes on EPI secretion was increased during CO. The mechanism of this apparent overcompensation by the cardiopulmonary receptors in 6-OHDA-treated cats is not clear. One could speculate that, in the sympathectomized heart, the increased afterload consequent to CO resulted in an increase in left ventricular end-diastolic pressure sufficient to stimulate the cardiac receptors and increase their inhibitory influence. Neither VB nor CO produced a significant change in plasma NE concentrations in 6-OHDA-treated cats, but the addition of the second manipulation to the first resulted in a significant increase in NE release. The response to VB was greater when VB was performed during CO, suggesting that the carotid sinus reflex was capable of attenuating the increase in plasma NE concentrations that would occur during VB. Since the adrenal gland is the only source of plasma NE in 6-OHDA-treated animals, it can be concluded that the carotid sinus and cardiopulmonary reflexes modulate the secretion of adrenal NE as well as EPI.

It is likely that, even in animals with intact sympathetic nerves, plasma NE concentrations in the present study represent predominantly adrenal NE for the following reasons: (1) plasma samples were obtained near the origin of the adrenal vein, and (2) changes in arterial pressure due to either CO or VB alone were not accompanied by changes in plasma catecholamine concentrations, suggesting that locally released NE, rather than circulating catecholamines, was responsible for the pressor responses.

The same type of interaction seen in the present study with regard to catecholamine secretion has been reported for the other humoral systems involved in the regulation of the circulation. Thames and Schmid (1979) reported potentiated responses in antidiuretic hormone (AHD) secretion upon sectioning either the carotid sinus or vagus nerves when the other input had been eliminated previously. Also, the interaction of cardiopulmonary and carotid sinus baroreceptors in the control of renin secretion is similar to that seen with catecholamine secretion in the present study (Jarecki et al., 1978; Thames et al., 1978).

In summary, the hemodynamic responses to CO, VB, and the combination of the two in this study are in general agreement with those reported in other studies. The changes in plasma catecholamine concentrations reflect the hemodynamic changes with regard to the interaction between the two reflexes. Therefore, it appears that a significant interaction occurs between the carotid sinus and cardiopulmonary reflexes in the modulation of adrenal catecholamine release.

It is difficult to determine the contribution made by adrenal catecholamines to the circulatory adjustments mediated by the carotid sinus and cardiopulmonary reflexes in animals with an intact sympathetic nervous system. However, the data from 6-OHDA-treated animals suggests that, in cases where the efferent sympathetic nervous system is impaired or
absent, adrenal catecholamines can become important in maintaining blood pressure.

The most important effects of circulating catecholamines may be on the heart. It has been shown that electrical stimulation of cardiac sympathetic effector nerves produces an increase in vagal afferent nerve traffic (Muers and Sleigh, 1972) and augments the inhibitory reflex responses mediated through the vagi (Shimizu et al., 1979). Intravenous epinephrine has been shown to activate cardiac receptors with afferent fibers in the vagi, not only through increases in arterial and left ventricular pressure, but also by its positive inotropic action (Sleigh and Widdicombe, 1965; Oberg and Thoren, 1972). Also, in the conscious dog, VB potentiates the inhibitory response of intracoronary catecholamines, suggesting that vagal afferents attenuate the effects of catecholamines through withdrawal of cardiac effector activity (Barron and Bishop, 1981).

Studies such as these have led to the concept of a negative feedback system which regulates myocardial contractility. (Fox et al., 1977; Shimizu et al., 1979; Barron and Bishop, 1981). Increases in cardiac sympathetic nerve activity would increase cardiac vagal afferent activity, which would then decrease sympathetic outflow to the heart and buffer the increases in contractility. The present study suggests that, in addition to efferent sympathetic nerve activity, circulating catecholamines could be involved in this cardiocardiac inhibitory reflex with its afferent limb in the vagi.

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