Direct Effects of \( \alpha_2 \)-Adrenergic Receptor Stimulation on Intravascular Systemic Capacity in the Dog

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SUMMARY The role of \( \alpha_2 \)-adrenergic receptor stimulation in the regulation of systemic vascular capacity and venous return, a major determinant of cardiac output, is not well understood. With the influence of the central nervous system isolated from the systemic circulation, the direct peripheral vascular effects of two specific, chemically distinct \( \alpha_2 \)-adrenergic receptor agonists, UK 14,304 and B-HT 920, were investigated in 19 dogs on total cardiopulmonary bypass with constant arterial perfusion and central venous pressure. Five-minute intra-arterial infusions of UK 14,304 (200 \( \mu \)g/min) resulted in increased arterial resistance (mean arterial pressure increased 18 \( \pm \) 4 [SEM] mm Hg; \( p<0.01 \)) and a decrease in systemic vascular capacity (81 \( \pm \) 20 ml; \( p<0.01 \)). This decrease in systemic vascular capacity appears to result from vasoconstriction, since there was no decrease in transhepatic resistance to portal flow and no significant change in hepatic vein flow to suggest redistribution of arterial blood flow. Yohimbine abolished both the arterial and systemic capacity effects, whereas prazosin did not. Intra-arterial administration of B-HT 920 (200 \( \mu \)g/min) in five dogs produced similar changes in arterial resistance and systemic capacity. These findings provide direct evidence for \( \beta_2 \)-adrenergic control, not only of arterial resistance but also of systemic vascular capacity, which in the intact animal would increase venous return to the heart. (Hypertension 11: 352-359, 1988)

KEY WORDS • UK 14,304 • B-HT 920 • yohimbine • canine

THE importance of the regulation of systemic vascular capacity, which in turn determines venous return to the heart and thus cardiac output, has been a subject of recent investigation. \( \beta \)-Adrenergic receptor stimulation has been shown to decrease vascular capacity, and acetylcholine infusion and parasympathetic nerve stimulation have been shown to increase vascular capacity. The role of \( \alpha \)-adrenergic stimulation in the regulation of systemic vascular capacity is less well understood. Postsynaptic \( \alpha_2 \)-adrenergic receptors have been demonstrated in the veins and arteries of several mammalian species in vitro. Previous studies have also shown that there is a predominance of \( \alpha_2 \)-adrenergic receptors in veins, suggesting that the stimulation of these receptors may importantly influence venous return. The development of selective \( \alpha_2 \)-adrenergic receptor agonists permits more detailed investigation of the direct effect of \( \alpha_2 \)-adrenergic stimulation on the capacitance circulation.

In the pithed rat, Gerold and Haeusler have shown that the administration of three distinct \( \alpha_2 \)-agonists results in an increase in both systemic vascular resistance and cardiac output. The latter effect is consistent with an increase in venous return secondary to constriction of the capacitance vasculature. Kalkman et al. also noted an increase in cardiac output following B-HT 920 administration to the pithed rat. In the former study, calcium antagonists blocked the vascular resistance response to \( \alpha_2 \)-agonist administration, but in both studies the administration of calcium antagonists failed to block the increase in cardiac output. Furthermore, in the latter study, the administration of the \( \alpha_2 \)-agonist B-HT 920 to the pithed cat failed to increase cardiac output. Thus, in the cat venoconstriction cannot be
Elicited by stimulation of postjunctional $\alpha_2$-adrenergic receptors. There appears to be a species difference with regard to the hemodynamic effects of $\alpha_2$-adrenergic receptor stimulation in the capacitance vasculature.

Following spinal cord transection and ganglionic blockade in dogs, the $\alpha_2$-agonist B-HT 933 failed to increase cardiac output. $\alpha_2$-Adrenergic stimulation inhibits impulses from the vasomotor center through the anterolateral spinal column to the sympathetic nervous system and also from the nucleus of the solitary tract. In addition, stimulation of presynaptic $\alpha_2$-adrenergic receptors results in inhibition of norepinephrine release at the synaptic cleft. Both of these effects result in decreased arterial resistance and arterial hypotension, which may mask the direct effects on the systemic circulation of $\alpha_2$-adrenergic receptor stimulation. The present studies were undertaken to examine the effect of direct $\alpha_2$-adrenergic receptor stimulation on the peripheral vasculature in a preparation surgically devoid of the effect of central nervous system modulation. Under conditions of controlled hemodynamics, the direct peripheral effects on vascular capacity and arterial vascular resistance of the specific $\alpha_2$-agonists UK 14,304 (5-bromo-6-[2-imidazolin-2-ylamino]-quinoxaline) and B-HT 920 (6-allyl-2-amino-5,6,7,8-tetrahydrazol-4H-thiazolo-[4,5-d] azepine) were investigated. The experimental protocol allowed quantification of the changes in intravascular volume produced by the direct peripheral effects of $\alpha_2$-adrenergic receptor stimulation.

Materials and Methods

Nineteen adult mongrel dogs of either sex weighing between 18 and 25 kg were anesthetized with chloralose (90 mg/kg i.v.) and urethane (900 mg/kg i.v.). After endotracheal intubation, ventilation was accomplished with a Bird Mark VII constant pressure respirator (Palm Springs, CA, USA) with 100% oxygen. A right-sided lateral thoracotomy and a midline abdominal incision were performed. The total cardiopulmonary bypass preparation with the central nervous system isolated is shown in Figure 1. After the administration of heparin (3 mg/kg i.v.), the femoral veins and superior vena cava were cannulated and the azygos vein was ligated. The venous blood from these veins was directed through an overflow column, the height of which was set to produce a venous pressure of 8 cm H$_2$O, to a Harvey Bubble Oxygenator (Model H-1000, C.R. Bard International, Murray Hill, NJ, USA) and heat exchanger (37 ± 0.5°C) and returned through a variable speed, calibrated roller pump (Cardiovascular Instruments, Wakefield, MA, USA) to the femoral arteries. To exclude the pulmonary, bronchial, and coronary circulation, the aorta (2 cm above the aortic valve) and the pulmonary hili were cross-clamped. Drains were placed in the right and left ventricular cavities to ensure the adequacy of the cross-clamping. A constant rate of pumping into the femoral arteries was maintained throughout each experiment. The inferior vena cava was ligated just below the liver and cannulated in the chest in retrograde fashion to drain the hepatic venous outflow separately. The hepatic venous outflow was also directed through an overflow column, the height of which was set at 8 cm H$_2$O. The hepatic venous blood was then returned to the oxygenator. In an attempt to have the model more closely simulate the human vascular system, splenectomy was performed to eliminate the possible influence of the muscular capsule of the dog spleen on vascular capacity.

Since $\alpha_2$-adrenergic receptor stimulation is known to have a central effect, the influence of the central nervous system was eliminated from these preparations. In the majority of the animals this was accomplished by surgically sectioning the spinal cord in the neck and sectioning the carotid sinus nerves. To obtain a more physiological state, in three animals the spinal cord was not sectioned but the central nervous system was perfused with blood not containing an $\alpha_2$-agonist. To
accomplish this, the carotid arteries were cannulated and perfused from a separate oxygenator, the vertebral arteries were ligated, and the drainage from the internal jugular veins was returned to the carotid perfusion oxygenator. The cervical vagi were sectioned in the neck to prevent possible contribution of the parasympathetic nervous system to the observed results. Thus, no neurogenic transmission could occur. Bilateral adrenalectomy was also performed.

All pressures were measured with Statham P23Db transducers (Oxnard, CA, USA); the frequency response of the pressure measurements system was linear up to 30 cps. Systemic and carotid (in the three animals with separate carotid perfusion) arterial pressures were measured through a short cannula placed in the left brachial artery and in a branch of the external carotid artery, respectively. Portal vein pressure was measured from the cannula inserted into a branch of the splenic vein and advanced into the portal vein. Hepatic vein and central venous pressures were measured at the base of their respective overflow columns. All measured pressures were recorded on a Hewlett-Packard 7700 eight-channel recorder (Waltham, MA, USA).

Hepatic vein flows of 20 seconds' duration were manually collected in graduated cylinders. Transhepatic resistance was calculated from the difference between portal vein pressure and hepatic vein pressure divided by the hepatic vein flow. Arterial resistance was calculated from the difference between mean arterial pressure and central venous pressure divided by the total cardiac output.

The systemic oxygenator was calibrated with a scale of 20-ml increments (from 0–2000 ml) before each experiment. When dogs are placed on total cardiopulmonary bypass, the oxygenator blood volume progressively falls; in the absence of interventions, this reduction is linear over time. Computer-assisted regression lines were drawn through the control period, and the lines were extrapolated for oxygenator blood volume throughout the study, as previously described. Changes produced by an intervention were measured as the differences between the extrapolated regression line and the observed oxygenator volume at each point in time. The reciprocal of each change in oxygenator volume represented a change in total systemic vascular capacity.

The justification of this extrapolation was verified previously in 10 experiments,27 all with 11 distinct, equally spaced sample points in a 10-minute control period. Straight lines were fit to the control period points, and variances in the estimated regression lines were computed for each minute postcontrol out to the full 20-minute experimental protocol. The standard estimates for variance in the prediction of a population regression line were employed.28 These minute by minute variance estimates, which result in hyperbolic confidence belts around the straight line that is extrapolated from the control period into the experimental period, were then pooled across all 10 experiments at each minute using the standard method for pooling variance estimated from independent sources.29 The pooled minute by minute variance estimates were then used to construct confidence limits (67% SEM) about the x-axis of the hypothetical zero change in volume.

In 10 animals, 5-minute infusions of UK 14,304 (Pfizer), 200 μg/min in normal saline at a concentration of 100 μg/ml, into the systemic arterial system (see Figure 1) were performed. The infusions were administered at 2 ml/min with a constant infusion pump (Model 600-900-5, Harvard Apparatus, Dover, MA, USA).

In eight of these animals UK 14,304 was infused again following the administration of prazosin (0.3 mg/kg; Pfizer). The adequacy of α₁-adrenergic receptor blockade with prazosin was tested by assessing the arterial pressure response to 100-μg intra-arterial injections of phenylephrine (Neosynephrine, Winthrop Laboratories). In these eight animals, yohimbine (1 mg/kg; Sigma Chemical) was subsequently administered and repeat 5-minute infusions of UK 14,304 were performed.

To examine the effects of direct α₁-adrenergic stimulation on the peripheral vasculature, UK 14,304 was infused into the femoral artery perfusion cannula at 200 μg/min in two animals after evisceration. In these animals the entire splanchnic viscera including the liver, stomach, and intestines had been removed.

Five animals received B-HT 920 (Boehringer Ingelheim) infusions (200 μg/min in normal saline at a concentration of 100 μg/ml) into the systemic arterial system (see Figure 1). Repeat infusions of B-HT 920 at 200 μg/min were performed in two animals following α₁-adrenergic receptor blockade with yohimbine (1 mg/kg) and in two animals following combined adrenergic receptor blockade with prazosin (0.3 mg/kg) and yohimbine (1 mg/kg).

The significance of measured parameters as compared with control values was determined by analysis of variance and covariance including repeated measures.30 Individual data points also were tested for significance using a double-tailed, paired t test. Significance was assumed only at a p value below 0.05. For the vascular volume comparisons, individual data points were tested using an unpaired t test. In each case, four time points were tested and significance was assumed only at a p value below 0.0125. The Bonferroni correction for multiple comparisons was used for both vascular volume and the remainder of the hemodynamic comparisons.31 Values are given as means ± SEM.

Results

Figure 2 shows the mean hemodynamic data obtained in 10 animals given 5-minute infusions of UK 14,304. As shown in Figure 2A, total systemic vascular volume decreased during the infusion: After 5 minutes of infusion there was a volume loss of 81 ± 20 ml (p<0.01). Following termination of the infusion, the slope of the decrease in total vascular volume lessened and then plateaued. Of this group, three animals had separate perfusion and drainage of the carotid arteries.
Effects of \( \alpha_2 \)-adrenergic receptor stimulation

**Figure 2.** Mean effects of 5-minute intra-arterial infusions of UK 14,304 in 10 animals. A. Total vascular volume decreased in response to the infusion of the \( \alpha_2 \)-agonist. B. Mean arterial pressure increased significantly in response to UK 14,304 and transhepatic resistance to portal blood flow, central venous pressure (CVP), and hepatic vein flow did not change significantly.

and veins, and the decrease in vascular capacity was similar with volume decreasing by 65, 175, and 110 ml.

Mean arterial pressure (see Figure 2B) rapidly and substantially increased to 77 ± 6 mm Hg (\( p < 0.01 \)) from a control level of 59 ± 3 mm Hg in response to UK 14,304 and returned toward the control level but was still elevated 10 minutes after the termination of the infusion. Since a constant rate of perfusion (1400 ± 108 ml/min) into the femoral arteries was maintained in each dog, arterial resistance increased to 54 ± 7 mm Hg/L/min (\( p < 0.01 \)) from a control level of 40 ± 4 mm Hg/L/min in response to UK 14,304. The effect of UK 14,304 persisted following the termination of the infusion as the return toward control levels of both total vascular capacity and mean arterial pressure was minimal. Central venous pressure was constant at \( 8 ± 0.2 \) cm H\(_2\)O through an overflow column, and hepatic vein flow did not change significantly in response to \( \alpha_2 \)-adrenergic receptor stimulation with UK 14,304 (see Figure 2B). Thus, significant arterial redistribution either into or away from the splanchnic circulation did not occur. Transhepatic resistance to portal blood flow increased slightly (from 52.3 ± 14.9 to 58.8 ± 15.8 cm H\(_2\)O/L/min) but not significantly during the infusion of UK 14,304 (see Figure 2B). Following termination of the infusion, the transhepatic resistance continued to increase such that by 110 minutes after termination of the infusion it was 61.9 ± 17.4 cm H\(_2\)O/L/min (\( p < 0.01 \)).

In eight animals in which 5-minute infusions of UK 14,304 were performed following \( \alpha_1 \)-adrenergic receptor blockade with prazosin, total vascular capacity decreased by 57 ± 15 ml (\( p < 0.01 \)), as can be seen in Figure 3A. This change was not significantly different from the results obtained without prazosin blockade, although vascular capacity returned toward the control level following termination of the infusion. Mean arterial pressure increased in response to UK 14,304 infusions (from 63 ± 4 to 77 ± 7 mm Hg; \( p < 0.01 \)). Thus, \( \alpha_1 \)-adrenergic receptor blockade does not affect the increase in arterial resistance associated with UK 14,304 administration, since arterial perfusion (1450 ± 116 ml/min) was constant in each experiment. Similar to findings in the unblocked animals, central venous pressure and hepatic vein flow did not change significantly. Transhepatic resistance to portal blood flow again increased slightly but not significantly (from 73.5 ± 22.1 to 81.1 ± 24.4 cm H\(_2\)O/L/min).

In eight animals in which combined \( \alpha_1 \)-adrenergic (with prazosin) and \( \alpha_2 \)-adrenergic (with yohimbine) receptor blockade was instituted before 5-minute UK 14,304 infusions, the decrease in total vascular capacity was abolished (Figure 4A). During the infusions there was no significant change in total vascular volume (−13 ± 26 ml). Mean arterial pressure did not increase significantly in response to \( \alpha_2 \)-adrenergic stimulation with UK 14,304 following combined \( \alpha_1 \)- and \( \alpha_2 \)-adrenergic receptor blockade (Figure 4B). Since arterial perfusion (1512 ± 114 ml/min) was constant, arterial resistance also did not increase significantly in response to UK 14,304 in this group of animals. There was also no significant change in central venous pressure, hepatic vein flow, or transhepatic resistance to portal blood flow.

To investigate whether tachyphylaxis to \( \alpha_2 \)-adrenergic receptor stimulation with UK 14,304 occurred, sequential infusions of UK 14,304 were performed in
FIGURE 3. Mean effects of 5-minute intra-arterial infusions of UK 14,304 following selective α₁-adrenergic receptor blockade with prazosin in eight animals. A. Total vascular volume decreased significantly in response to UK 14,304 infusion and was not significantly different from the decrease observed before α₁-adrenergic receptor blockade. B. Similarly, mean arterial pressure increased in response to the α₂-agonist, and again, no significant change in transhepatic resistance, central venous pressure (CVP), or hepatic vein flow was noted.

FIGURE 4. Mean effects of 5-minute intra-arterial infusions of UK 14,304 following combined α₁- and α₂-adrenergic receptor blockade with prazosin and yohimbine in eight animals. A. Following the addition of α₂-adrenergic receptor blockade, there was no significant change in vascular volume in response to UK 14,304. B. Similarly, following the addition of α₂-adrenergic receptor blockade, mean arterial pressure did not increase significantly during the infusion of UK 14,304.
two animals. The observed decreases in vascular capacity were 135, 105, and 105 ml in one animal and 160, 105, and 60 ml in the other. The arterial pressure increases were 12, 6, 5 mm Hg and 6, 6 and 5 mm Hg with the sequential infusions in the first and second animals, respectively. Thus, tachyphylaxis alone to intra-arterial infusion of UK 14,304 would not account for the observed effects on total vascular capacity and arterial resistance following \(a_1\)- and \(a_2\)-adrenergic receptor blockade.

In two eviscerated animals, total vascular volume decreased by 50 and 54 ml in response to \(a_2\)-adrenergic receptor stimulation with a 10-minute infusion of UK 14,304. Mean arterial pressure increased from 64 to 85 mm Hg in one animal and from 50 to 59 mm Hg in the other in response to the infusion. Thus, arterial resistance increased, since arterial perfusion was constant at 1325 ml/min in each animal. Central venous pressure remained constant through the use of an overflow column at 8 cm H\(_2\)O.

Five animals underwent 10-minute infusions of the chemically distinct \(a_2\)-agonist B-HT 920. As seen in Figure 5, total systemic vascular volume decreased by 68 ± 25 ml \((p<0.01)\) in response to the infusion of B-HT 920. Mean arterial pressure increased from 61 ± 5 mm Hg to 88 ± 8 mm Hg \((p<0.01)\) during the infusion. The rate of arterial perfusion and central venous pressure \((8 ± 0.1 \text{ cm H}_2\text{O})\) remained constant in each animal. Hepatic vein flow increased \((513 ± 39 \text{ to } 564 ± 34 \text{ ml/min}; p<0.01)\) in response to the infusion of B-HT 920. Transhepatic resistance to portal blood flow also increased slightly \((24.3 ± 3.9 \text{ to } 29.1 ± 4.9 \text{ cm H}_2\text{O/L/min}; p<0.01)\) in response to the B-HT 920 infusion, which would tend to oppose a decrease in systemic vascular volume.

As shown on the right side of Figure 5, following either combined \(a_1\) - and \(a_2\)-adrenergic receptor blockade with prazosin and yohimbine \((n = 2)\) or only \(a_2\) -adrenergic receptor blockade with yohimbine \((n = 2)\), the decrease in total systemic vascular capacity in response to B-HT 920 was abolished, similar to the abolition of the response to UK 14,304 after \(a_1\) - and \(a_2\)-adrenergic receptor blockade. Of note is that in the two animals in which only \(a_2\)-adrenergic receptor blockade with yohimbine was instituted, vascular capacity did not decrease \((0 \text{ and } +40 \text{ ml})\). There was a small but significant increase in mean arterial pressure \((from \ 54 ± 5 \text{ to } 57 ± 5 \text{ mm Hg}; p<0.01)\) in response to B-HT 920 infusion following blockade, suggesting that complete blockade of the arterial circulation was not achieved. Preinfusion central venous pressure was \(8 ± 0.3 \text{ cm H}_2\text{O}\) and did not change. Hepatic vein flow did not change significantly in response to B-HT 920 infusion after blockade \((from \ 366 ± 38 \text{ to } 369 ± 77 \text{ ml/min})\), nor did transhepatic resistance change significantly during these B-HT 920 infusions after blockade.

**Discussion**

The present data demonstrate that direct \(a_2\)-adrenergic receptor stimulation in the systemic vasculature results in a substantial decrease in vascular capacity, as well as a significant increase in arterial resistance in the dog. Selective \(a_2\)-adrenergic receptor blockade verifies that these effects are mediated primarily through \(a_2\)-adrenergic receptor.
tor stimulation. Diffuse vasoconstriction in both the peripheral and splanchnic vasculature appears to be the mechanism whereby α₂-adrenergic receptor agonists decrease vascular capacity.

Total systemic vascular capacity decreased in response to α₂-adrenergic receptor stimulation, which in the intact animal would result in an increase in venous return to the heart. The effect must be due to direct α₂-adrenergic receptor stimulation, since the central nervous system regulation of the sympathetic nervous system (either directly or through a baroreceptor mechanism) and the possible contributing effects of the parasympathetic nervous system and the adrenal glands were prevented. The finding that prazosin only partially decreased the response and yohimbine blocked it demonstrates that the change in vascular capacity was predominantly due to α₂-adrenergic receptor stimulation alone and not entirely to α₁-adrenergic receptor stimulation.

It is unlikely that arterial redistribution or changes in transhepatic resistance to blood flow, both of which have been demonstrated to alter vascular capacity,1,4,33 account for the observed effect. Caldini et al.33 have shown that increased arterial inflow into the splanchnic vasculature, which has a slow venous time constant, can produce an increase in vascular capacity in that area. In the present study, however, systemic arterial perfusion was maintained at a constant level and the change in hepatic vein outflow was not significant with UK 14,304 infusion, making arterial redistribution of blood flow an unlikely cause of the decrease in capacity. If the mean increase in hepatic vein outflow after α₂-adrenergic receptor stimulation with B-HT 920 had resulted in an increase in splanchnic vascular capacity by the effect proposed by Caldini et al.,33 it would have tended to increase and oppose or minimize the observed decrease in systemic vascular capacity. Cholinergic receptor stimulation4 and β-adrenergic receptor stimulation2 regulate systemic vascular capacity in the dog through alterations in transhepatic resistance. In contradistinction, the role of transhepatic resistance in the α₂-adrenergic receptor-mediated control of vascular capacity, as shown by the present study, is minimal. There was a small increase in transhepatic resistance in response to α₂-adrenergic receptor stimulation, which would actually tend to pool blood in the splanchnic vasculature and increase systemic vascular volume. Since a decrease in systemic vascular capacity was observed, this is likely to be a direct effect and not due to arterial redistribution or changes in transhepatic resistance.

In the present study, as expected, arterial resistance increased in response to α₂-adrenergic receptor stimulation, demonstrating a direct arterial vasoconstrictor response. Previous studies have shown that the α-adrenergic receptors of veins are predominantly α₂-adrenergic receptors and differ from the α-adrenergic receptors of arteries both in their affinity for α-agonists and in their number. They also are affected to a lesser extent by the α₂-antagonist prazosin than by a selective α₂-antagonist.11-15 A recently published study by Segstro and Greenway13 demonstrated that the hepatic volume of the cat, monitored plethysmographically, decreases in the presence of an α₂-agonist. The finding by Eslner et al.20 that UK 14,304 decreases effective vascular compliance in the dog with ganglionic blockade also provides evidence for a direct hemodynamic effect of an α₂-agonist on the venous circulation. Evidence for the decrease in vascular capacitance found in the present study was not seen in the canine studies by Zandberg et al.18 and by Woodman and Vatner.19 The dose of the α₂-agonist employed in the present study was high compared with that used in either of the latter two studies but lower than that used by Eslner et al.16 Other studies have definitively demonstrated that there are postsynaptic α₂-adrenergic receptors in arteries of several mammalian species including humans, with both α₁- and α₂-adrenergic arterial receptors.5,14,34 Dog and humans appear to have both α₁- and α₂-adrenergic receptors in the arterial and venous circulations.10,14,35 The arterial vasoconstriction demonstrated in the present study was blocked by yohimbine and not by prazosin; therefore, there was a direct arterial constrictor response to α₂-adrenergic receptor stimulation. This arterial constriction may account for some of the observed total vascular capacity decrease, but it probably does not account for the majority of the effect, as previous studies have shown little change in vascular capacity when the venous system is not affected, despite the presence of major changes in arterial resistance.4

A second, chemically distinct α₂-agonist, B-HT 920, showed directionally similar results to those observed with the α₂-agonist UK 14,304. This finding suggests that the observed effects can be attributed to α₂-adrenergic receptor stimulation and are not just a nonspecific effect of UK 14,304. There appeared to be a redistribution of arterial flow to the splanchnic circulation with B-HT 920 but not with UK 14,304 infusion. This effect may be due to a greater selectivity of B-HT 920 for α₂-adrenergic receptors and may represent a difference in α₁- and α₂-receptor selectivity. Because of species differences, an extrapolation from the present data to humans must be done with caution. A variability in number and affinity of both presynaptic and postsynaptic α-adrenergic receptors in arteries and veins in many species has been demonstrated.5,10,14,15,35 The present study demonstrates that in the dog the response to α₂-adrenergic stimulation appears to have a substantial effect on both systemic capacity and arterial resistance.

This study was undertaken to examine the direct peripheral effects of α₂-adrenergic receptor stimulation. In a neurologically intact animal or human, α₂-adrenergic stimulation would likely decrease arterial resistance and result in hypotension rather than cause an increase in mean arterial pressure secondary to arterial vasoconstriction. In the present study, the hypotension is due to the centrally mediated effect of α₂-adrenergic stimulation, which results in sympathetic withdrawal.21-28 Withdrawal of sympathetic activity might also be expected to have a nega-
tive inotropic effect, which might be particularly pronounced in the presence of heart failure. The net effect on the capacitance system of a direct constrictor effect balanced against a central neural effect that would tend to increase intravascular capacitance remains to be documented.

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