Comparison of Effects of Angiotensin and Norepinephrine on Pulmonary Circulation, Systemic Arteries and Veins, and Systemic Vascular Capacity in the Dog

By John C. Rose, M.D., Peter A. Kot, M.D., Jay N. Cohn, M.D., Edward D. Freis, M.D., and Gerald E. Eckert, M.D.

The study of responses to drugs is rewarding to the cardiovascular physiologist. Many agents evoke integrated responses that involve the heart, the pulmonary circulation, the systemic arteries, and the veins. The challenge is to dissect these responses into their component parts—to discover the contributions to the overall change made by alterations in cardiac function and vasomotor activity in various regions. In this way, a clearer view is obtained of the ways in which the cardiovascular system can adjust itself to new demands, both physiologic and pathologic. In addition, these particular stimuli, drugs, can be understood more fully and used for their specific properties.

Norepinephrine and angiotensin are important, naturally occurring, potent pressor agents. While both raise the systemic arterial pressure, the integrated responses they evoke are quite different. These differences can be appreciated by examination of figures 1 and 2. The tracings represent the results of single rapid intravenous injections of these drugs into the femoral vein of an anesthetized, open-chest dog. Systemic arterial pressure, pulmonary arterial pressure, and left atrial pressure are recorded with strain gauges. Blood flow in the descending thoracic aorta is measured with an inserted ultrasonic flowmeter.

Let us assume, for purposes of this discussion, that thoracic aortic blood flow is proportional to cardiac output. The response to norepinephrine involves the typical catechol amine response in the myocardium. As systemic arterial pressure and cardiac output rise, left atrial pressure falls (fig. 1). Obviously, an immediately increased venous return has made available a source of blood for the greatly increased left ventricular output at a lower filling pressure. This integrated response to sympathoadrenal stimulation has been discussed in detail. It is further noted that the pulmonary arterial pressure begins to rise prior to the observation of effects on the heart and systemic circulation.

The pressor response to angiotensin II obviously involves different mechanisms (fig. 2). The rise in systemic arterial pressure is slower and accompanied, at first, by a depression of cardiac output. Left ventricular output then increases temporarily but only after left atrial pressure has increased. Pulmonary arterial pressure appears to rise in response to elevated left atrial pressure. While the responses illustrated here are not the results of precisely equipressor doses, it is evident that the catechol amine has a more direct myocardial effect than angiotensin II.

The studies described below are an attempt to dissect from these overall effects the responses of individual segments of the circulation—pulmonary vasculature, systemic arteries, and systemic veins. Numerical and methodologic details are omitted since these have been reported or will be reported elsewhere. The results suggest differing peripheral sites of action for norepinephrine and angiotensin II that may have clinical implications.

From the Department of Physiology and Biophysics and the Department of Medicine, Georgetown University School of Medicine, Washington, D.C.

This work was supported by a grant (H-1904) from the National Institutes of Health.
The Pulmonary Circulation

Figure 3 illustrates a left ventricular bypass procedure that permits the study of the peripheral vascular system in anesthetized dogs with a controlled left ventricular output. Blood is drained from the left atrium to a reservoir, from which it is pumped to the descending thoracic aorta. The left ventricle is completely bypassed, while the right ventricle continues to function effectively. The right side of figure 3 shows a modification of this technic that permits study of the direct effects of drugs on pulmonary blood vessels. As the drug under study is injected into the main pulmonary artery, the tube that drains the left atrium is diverted to a second, temporary reservoir (R2). For a period of 45 seconds or so, the systemic circulation is maintained normally with blood pumped from the previously filled main reservoir (R1). When the main reservoir is nearly depleted, the left atrial drainage tube is returned to its former

Figure 1

Tracing showing effects of rapid injection of norepinephrine into femoral vein of a dog. Paper speeds are 1 and 25 mm./sec. See text for explanation and discussion.
position in R1. During the period in which the left atrial tube is diverted to R2, the drug under study has traversed only the pulmonary circulation. Changes in pulmonary arterial pressure and pulmonary blood flow during this period are due only to alterations of pulmonary vascular resistance. Factors such as back-pressure from the left atrium and shifts of blood from systemic to pulmonary circulation are eliminated.

In this preparation, norepinephrine (3 to 10 μg./Kg.) produced a direct vasoconstrictor effect in the pulmonary vascular bed, with a rise in pulmonary arterial pressure and a decrease in pulmonary venous flow. A greater rise in pulmonary arterial pressure occurred when R2, the temporary reservoir containing the drug that had traversed the pulmonary vessels, was emptied back into the pump circulation. This rise was due to increased pulmonary blood flow.

Angiotensin II, on the other hand, had no
direct effect on pulmonary blood vessels. In doses capable of producing marked systemic pressor responses, there were no changes in pulmonary or systemic pressures or vascular resistances when this agent was confined to the pulmonary circulation. These studies indicated that the transient elevation of pulmonary arterial pressure that follows systemic administration of angiotensin II in dogs is due to factors other than pulmonary vasoconstriction, probably chiefly elevated left atrial pressure. This view was suggested in 1942 by Friedberg, Katz, and Steinitz. The recent studies of Sancetta in man support the notion of a "passive" response of the pulmonary arteriolar bed to angiotensin II.

Thus, confining norepinephrine and angiotensin II to the pulmonary circulation discloses qualitative differences in the effects of these agents on pulmonary blood vessels that adequately explain the early pulmonary arterial pressure changes in figures 1 and 2.

Systemic Vascular Capacity

The blood volumes in the central and peripheral systemic circulations form a reciprocating system. Shifts of blood from one area to the other are important in circulatory adjustments to physiologic and pharmacologic stimuli. The major role of the systemic venous system as an active and changing reservoir in this regard is well known.

By means of the experimental circuit shown on the left in figure 3, norepinephrine has been used to mimic sympathetic vasomotor activity. Shifts of blood into or out of the intravascular compartment of the dog were determined by monitoring changes in the blood level of the pump reservoir. Rapid injections of norepinephrine (1 to 7 μg./Kg.) constricted the total vasculature and decreased vascular volume by 8 to 24 per cent.

Angiotensin II, 1 μg./Kg., and norepinephrine, 2 μg./Kg., were compared with this technic. These doses provided approximately equipressor responses in the pump preparation when given rapidly intravenously. The profound differences between these agents when studied in the same dogs are illustrated in figure 4. Norepinephrine produced a rapid reduction in intravascular volume, up to 8.5 per cent of total blood volume in 2.5 minutes. In contrast, angiotensin II caused a minimal increase in intravascular volume. Responses to continuous infusions of drugs produced the same results.

These divergent effects on systemic vascular capacity explain in part the differences in blood flow responses to angiotensin II and norepinephrine noted in figures 1 and 2. Acute reduction of systemic vascular capacity by norepinephrine "squeezes" blood into the central circulation, making an increased ve-

Figure 3

Diagrams of left ventricular bypass procedures. On the right is the system for study of drugs temporarily confined to the pulmonary circulation. Drugs are injected into the pulmonary artery at (I). Aorta (AO), air trap (AT), left atrium (LA), pump (P), reservoir (R). See text for details. (Courtesy of American Journal of Physiology)
nous return immediately available. No source of blood is immediately available to provide for an increased cardiac output in the case of angiotensin II. (This factor, of course, is considered here independently of direct myocardial stimulation or the lack of it.)

Veins Versus Arteries

The capacity of the systemic venous reservoir is altered by changes in venomotor tone. The widely divergent effects of angiotensin II and norepinephrine on systemic vascular capacity suggested that these drugs have different effects on veins. This suggestion has been corroborated to some extent by the simple expedient of applying the drugs topically to intact but occluded segments of femoral and mesenteric arteries and veins. Segments of these vessels were exposed and occluded for lengths of about 5 cm. by small, noncrushing clamps. Pressures within the segments were adjusted to normal intravascular levels and then continually recorded. Elevation of intrasegment pressure indicated smooth muscle contraction.

All arterial segments responded to both norepinephrine and angiotensin II. The concentrations required were as high as 50 μg./ml. (5 drops), and norepinephrine responses were more rapid. Differences in arterial responses may be due to permeability factors and molecular size.

On the other hand, there were marked qualitative differences in the responses of veins. All veins constricted vigorously and rapidly with topically applied norepinephrine in concentrations as low as 1 μg./ml. (2 drops). Angiotensin II in concentrations as high as 500 μg./ml. failed to show any effects on veins. These differences were consistent in all vessels studied.8

These vessel segment studies are subject to criticism on several counts, such as the size of the vessels studied, their role in systemic vascular capacity adjustment, and differences between angiotensin II and norepinephrine with regard to molecular size, permeability, and rates of destruction. However, they tend to corroborate the view that norepinephrine reduces systemic vascular capacity through its venoconstrictor effect, while failure of angiotensin II to reduce systemic vascular capacity is due to its inability to cause venoconstriction.

This view receives substantial support from the abstract of Folkow and his colleagues.9 Using different methods, these authors determined that the precapillary vessels of cats were more responsive to the constrictor effects of angiotensin II than norepinephrine. On the other hand, in equipressor doses, the amount

---

*Figure 4*

*Chart showing alterations in vascular volume following rapid injections of both norepinephrine and angiotensin II in 10 dogs. Vertical lines represent standard deviations. Volumes expressed as per cent of an assumed total blood volume of 82 ml./Kg.*
of blood mobilized from the veins by norepinephrine was nearly 4 times as large as that mobilized by angiotensin II. These authors proposed that the smooth muscle of veins and arteries are supplied with norepinephrine receptors, while angiotensin II receptors are confined to precapillary vascular smooth muscle.

Summary
In dog experiments, angiotensin II and norepinephrine were compared in regard to some components of the generalized pressor response each of these agents produces. It was found that angiotensin II has no direct effect on pulmonary blood vessels, in contrast to the pulmonary vasoconstrictor effect of norepinephrine. Angiotensin II appeared to have no effects on veins or the systemic vascular capacity, while norepinephrine was a potent vasoconstrictor with, therefore, a marked ability to reduce the systemic vascular capacity.

References
Comparison of Effects of Angiotensin and Norepinephrine on Pulmonary Circulation, Systemic Arteries and Veins, and Systemic Vascular Capacity in the Dog

JOHN C. ROSE, PETER A. KOT, JAY N. COHN, EDWARD D. FREIS and GERALD E. ECKERT

_Circulation_. 1962;25:247-252
doi: 10.1161/01.CIR.25.1.247

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1962 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/25/1/247

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/