Influence of Carotid Baroreceptors and Vasoactive Drugs on Systemic Vascular Volume and Venous Distensibility

By John Ross, Jr., M.D., Charles J. Frahm, M.D., and Eugene Braunwald, M.D.

With the technical assistance of Mr. Robert M. Lewis

The importance of the carotid and aortic baroreceptors in the reflex control of heart rate, peripheral vascular resistance, and myocardial contractility is well appreciated. It has long been suspected that an important additional factor in circulatory regulation is the distensibility and capacity of the venous bed.1-6 The multiple circulatory effects of the baroreceptors have made precise study of their influence on total systemic vascular volume and on venous distensibility difficult. Nevertheless, several investigators have demonstrated changes in the capacity of isolated venous segments resulting from activation of carotid sinus receptors,7-13 and other studies have suggested that such reflexes may affect the entire venous bed.14, 15

The present investigation was carried out in an experimental preparation from which the heart and pulmonary circulation were excluded by means of total body perfusion. First, it was designed to permit study of the effects of alterations in pressure in the isolated carotid sinuses on the volume of the total systemic vascular bed and on venous return. Second, a method was devised for the determination of pressure-volume relationships in the systemic veins by briefly occluding the total venous outflow while inflow was held constant. This technique was utilized to study the effects of carotid sinus activation on the distensibility of the venous bed. In the past, similar approaches to the measurement of venous distensibility have included only portions of the total venous bed.11, 12 Finally, a comparison was made between the reflexly induced changes in: (1) systemic vascular volume, (2) venous return, and (3) the distensibility of the venous bed and those resulting from the action of known vasoconstrictor and vasodilator drugs.

Methods

Nineteen dogs weighing between 10.8 and 23.3 Kg., averaging 17.0 Kg., were studied under morphine (2 mg./Kg.), chloralose (48 mg./Kg.), and urethane (480 mg./Kg.) anesthesia. Heparin (2 mg./Kg.) was employed as an anticoagulant. Following a right thoracotomy, complete cardiopulmonary bypass was instituted (fig. 1). Blood was diverted from the venae cavae through large-bore rigid cannulae into a rotating disc oxygenator. Arterialized blood was returned through a recording rotameter to the femoral artery at a constant rate by means of a roller pump. The perfusion rates ranged from 67 ml./Kg. to 118 ml./Kg., and averaged 94 ml./Kg. The aorta was occluded above the coronary arteries in order to eliminate the heart and coronary circulation from the preparation, and bronchial arterial flow was returned to the extracorporeal circuit through drainage tubes placed into both atria.

Pressures were measured in the aorta, inferior vena cava, and superior vena cava through plastic catheters inserted into small branches of the femoral artery and vein, and into the external jugular vein. In six dogs, pressures in both carotid sinuses were measured through the superior thyroid arteries. Pressures were measured with Statham pressure transducers and recorded together with total systemic flow on a direct-writing oscillograph.

In two experiments (dogs nos. 1 and 5), carotid sinus pressure was altered by varying the rate of perfusion of the cannulated common carotid arteries. In these two dogs in which the carotid sinuses were not isolated, the carotid perfusion line originated at a point between the pump and the rotameter, and blood flow to the remainder of the animal could therefore be maintained constant. Carotid perfusion was altered by means of a screw clamp. Since blood flow to the carotid arteries was varied in order to change carotid sinus pressure, alterations in superior vena caval outflow occurred and valid venous occlusion curves
ROSS, FRAHM, BRAUNWALD

Figure 1
Schematic representation of the extracorporeal circuit employed. Blood drains by gravity from the superior vena cava (SVC) and the inferior vena cava (IVC) into the oxygenator. The clamp used for occlusion of the venous line (V.o.c.) is shown. The aorta (Ao) is cross-clamped above the coronary arteries. Drainage lines from the right and left atria (RA, LA) are drawn in black. Oxygenated blood is pumped through a rotameter (Rot.) into the femoral artery (F.A.). The line for perfusion of the carotid sinuses (C.S.) originates between the pump and rotameter and the perfusate is returned to the oxygenator through an accessory reservoir (access., not shown). The level of blood in the oxygenator is sensed by the detecting electrodes (Det.) and blood is added to or withdrawn from the calibrated reservoir (Res.).

could therefore be obtained only from the inferior vena cava. In addition, alterations in the flow of blood to the head produced changes in the volume of blood contained in this segment of the circulation, thus precluding measurement of the reflex effects of carotid sinus stimulation on intravascular blood volume.

To obviate these experimental limitations, complete isolation of both carotid artery bifurcations was carried out in four dogs (nos. 6, 8, 18, and 19) in a manner similar to that described by Heymans and Bouckaert.17 The common carotid arteries were cannulated immediately proximal to their bifurcations and the external carotid arteries were cannulated distally (fig. 1). The internal carotid arteries were ligated distal to the bulb as were all other large branches between the cannulae; care was taken to avoid injury to the carotid sinuses and their nerves. The carotid bodies were not denervated. Perfusion of the sinuses was carried out by the arterial pump through tubing which originated from a T tube placed between the pump and the rotameter. The pump provided phasic flow to the carotid sinuses. The perfusate was returned from the cannulated external carotid arteries to the venous end of the oxygenator and variations in perfusion pressure were achieved by modifying the resistance of this outflow line with a screw clamp.

In all six dogs in which carotid sinus perfusion pressure was altered, bilateral cervical vagotomy was performed in order to minimize the buffering effects of the aortic pressure receptors. In three dogs, epinephrine was infused into the arterial end of the oxygenator by a constant infusion pump at a rate of 1.5 μg./Kg./min.; in nine dogs, norepinephrine was infused at rates ranging from 1.5 to 3.8 μg./Kg./min., averaging 2.4 μg./Kg./min.; in six dogs, trimethaphan (Arfonad) was administered at rates ranging between 0.014 mg./Kg./min. and 0.057 mg./Kg./min., averaging 0.026 mg./Kg./min.; in two dogs, acetyleholine was infused at rates of 0.033 mg./Kg./min. and 0.038 mg./Kg./min.

Continuous measurement of alterations in the volume of blood in the extracorporeal circuit was carried out in each experiment; changes in the level of blood in the oxygenator were detected by sensing electrodes18 and blood was added to or removed from a calibrated reservoir so that the volume of blood in the oxygenator remained constant.19 Alternations in extracorporeal blood volume, which reflected reciprocal changes in the intravascular blood volume, were measured at one-minute intervals. In eight experiments, alterations in the intravascular blood volume were prevented by modifying the output of the pump; this maneuver permitted an estimation of the effects of any intervention on venous return. For example, when venous return to the oxygenator diminished, the pump output was decreased manually at a rate sufficient to maintain the volume of the extracorporeal circuit constant.19

Changes in venous distensibility were studied by measuring pressures in the superior and inferior vena cavae during sudden, brief occlusions of the venous outflow line while arterial inflow was maintained constant (fig. 1). During a steady state, venous return to the oxygenator equaled the output of the pump and it is assumed that blood entered the venous segment of the circulation at an identical rate. When, under these circumstances, the venous outflow is briefly occluded, the pressure in the venous system rises abruptly. The rate of this pressure elevation is primarily a function of the initial volume of the venous bed, its distensibility, and the rate of blood flow into it; since the latter was held constant throughout any given experiment, the influence of flow rate, as well as of any effects due to the inertial and viscous properties of the vessel walls, was minimized. The steady state was assured by performing the venous occlusions only after the transient

Circulation Research, Volume IX, January 1961
alterations in venous return accompanying the intervention under study had been completed and at a time when arterial pressure was stable.

The venous occlusion curves were analyzed by measuring the time interval required for the venous pressure to reach 30 cm. H2O following occlusion. This value will be referred to as the VR (venous-rise) time. In some experiments, small alterations in venous pressure occurred following an intervention. In calculating the VR times, the pressure-volume curve was extrapolated to the initial venous pressure obtained during the control period. The VR times obtained sequentially at three-minute intervals during the control periods varied by 0 to 6 per cent and averaged 2.8 per cent of the initial VR time. Since shorter time intervals between successive curves sometimes resulted in a progressive diminution of the VR time, a minimum of three minutes between curves was always allowed. Alterations in the VR times following each intervention were expressed as a percentage change of the mean of the two curves obtained during the control period.

Prior to applying this technique in the experimental animal it was tested in a simple model system. This consisted of a pump which delivered water through a segment of rigid tubing having a small volume and a screw clamp at its distal end to provide alterations in resistance. This “arterial segment” was connected to a distensible rubber bladder having a relatively large volume to simulate the venous portion of the circulation. Pressures were measured in both the “arterial” and the “venous” segments. A flowmeter placed between the pump and the “arterial” segment assured a constant flow of water through the system. It was observed consistently that when outflow was occluded the VR time was not influenced by the level of pressure in the “arterial” segment, but was modified by changes in flow rate and by alterations in the distensibility of the rubber bladder produced by employing tubes of varying wall thicknesses.

Results

The results* of the infusion of epinephrine and norepinephrine were similar. In the seven dogs in which changes in intravascular blood volume were determined, a shift of blood into the oxygenator began in the first two minutes after the onset of the infusion and was completed within six minutes. These shifts represented decreases in intravascular blood volume ranging from 8.6 to 37.0 mL/Kg. and averaged 19.0 mL/Kg. of body weight. In four experiments in which extracorporeal blood volume was held constant, during catecholamine infusion it was necessary to increase the output of the pump by 380 mL/min. to 630 mL/min. This represented 25 mL/Kg./min. to 43 mL/Kg./min., or 26 per cent to 64 per cent (average 40 per cent), of the control perfusion rates.

In the five experiments in which venous occlusion curves were obtained following infusion of catecholamines, the VR times in the inferior vena cava lengthened by 10 per cent to 190 per cent with an average prolongation of 68 per cent of the control value. Similarly, the VR times in the superior vena cava lengthened by 15 per cent to 110 per cent with an average prolongation of 47 per cent of the control values. Tracings obtained during a representative experiment are reproduced in figure 2. It was noted that the curves

*Complete tabulation of this data has been deposed as Document number 6399 with the ADI Auxiliary Publications Project, Photoduplication Service, Library of Congress, Washington 25, D. C. A copy may be obtained by citing the Document number and by remitting $1.25 for photoprints, or $1.25 for 35 mm. microfilm. Advance payment is required. Make checks or money orders payable to: Chief, Photoduplication Service, Library of Congress.
usually assumed a more sigmoid shape during epinephrine or norepinephrine infusion and resumed their original shape and slope upon discontinuing the drugs.

When trimethaphan was infused, the results were opposite to those observed with epinephrine or norepinephrine; in four dogs intravascular blood volume increased from 13.1 to 22.9 ml./Kg., averaging 17.3 ml./Kg. body weight. In the three experiments in which extracorporeal blood volume was held constant, it was necessary to diminish the pump output by 200 ml./min. to 630 ml./min. This represented a decline of 11 ml./Kg./min. to 36 ml./Kg./min. or 15 per cent to 42 per cent (average 30 per cent) of the control perfusion rates. In three experiments, the VR times in the inferior vena cava during trimethaphan infusion were diminished by 14 per cent to 24 per cent, and averaged 18 per cent less than control. The VR times in the superior vena cava diminished 23 per cent and 29 per cent, respectively, in two experiments (fig. 3).

In the two dogs in which acetylcholine was infused, intravascular blood volume diminished 19.8 and 6.1 ml./Kg. The VR times lengthened by 52 per cent and 36 per cent in the inferior vena cava and by 28 per cent and 23 per cent in the superior vena cava.

In the four dogs in which perfusion of the isolated carotid sinuses was performed, elevation of carotid sinus pressure resulted in a reflex fall in arterial pressure which ranged from 23 mm. Hg to 50 mm. Hg. At a constant perfusion rate, these changes reflected proportional decreases in peripheral vascular resistance which ranged from 31 per cent to 50 per cent and averaged 40 per cent of control resistances. The decline in pressure was accompanied by a shift of blood from the extracorporeal circuit resulting in an augmentation of intravascular blood volume averaging 12.9 ml./Kg. body weight and ranging from 190 ml. to 300 ml. (table 1; fig. 4).

In the five dogs in which venous occlusion curves were obtained, following an elevation in carotid sinus perfusion pressure the VR times in the inferior vena cava shortened by 21 per cent to 59 per cent with an average shortening of 35 per cent of control values. In the superior vena cava (four dogs), the VR times shortened by 28 per cent to 33 per cent with an average shortening of 31 per cent of the control values (fig. 4).

When carotid sinus pressure was diminished, arterial pressure rose by 12 mm. Hg to 39 mm. Hg. These changes represented in-
crease in vascular resistance which ranged from 13 per cent to 55 per cent and averaged 41 per cent of the control resistances. A shift of blood into the extracorporeal circuit occurred, representing a decrease in intravascular blood volume ranging from 50 ml. to 230 ml. In each instance, the venous occlusion curves were prolonged following the volume shift (table 1). In the inferior vena cava the VR times lengthened by 18 per cent to 56 per cent (average 20 per cent), while in the superior vena cava they increased 20 per cent to 50 per cent (average 35 per cent). In one experiment, in order to compensate for the increase in venous return accompanying carotid sinus hypotension, it was necessary to increase pump output by 27 per cent of the control level (fig. 5).

**Discussion**

Several investigators have demonstrated that sympathomimetic amines produce a contractile response of excised vein segments. Rashkind and associates, employing a preparation in which a reservoir and pump were interposed between the venae cavae and right atrium, demonstrated that blood was displaced into the reservoir following the administration of epinephrine. Similarly, in a preparation in which a reservoir and pump replaced the left ventricle, Rose and Freis showed that the volume of blood in the reservoir was augmented following norepinephrine infusion and declined after injection of hexamethonium. In both of these investigations, displacement of blood from the venous bed into the heart and pulmonary vascular bed could not be excluded. In addition, drug-induced changes in myocardial contractility, heart rate, and intracardiac pressure occurred. These factors, acting directly and perhaps through reflexes originating within the heart and lungs as well, undoubtedly modified the volume of blood returning to the reservoir. In contrast, in the preparation employed for the present experiments, the heart and lungs were completely excluded and measurements could be made both of the total systemic vascular capacity and of the shape of the pressure-volume curve of the venous bed.

*Figure 4*

Venous occlusion curves inscribed at a low (left) and at an elevated (right) pressure in the isolated carotid sinuses. The graph at the bottom of the figure indicates the time of occurrence and the magnitude of the reflex increment in intravascular blood volume which resulted from carotid sinus hypotension.

The large magnitude of the alterations in the systemic vascular volume observed in the present experiments suggests that the major changes in capacity occurred in the post-capillary or venous bed. The importance of the changes in the venous return accompanying these shifts in blood volume is indicated by the large modifications of the output of the pump which were necessary to obviate alterations in intravascular blood volume. These changes in pump output are analogous to the alterations in cardiac output which would have occurred had the heart responded passively to the volume of blood returned by the venous system and had the intervention under study produced no effect on the heart per se.

In interpreting the changes in the venous occlusion curves, it is helpful to refer to the studies of Alexander who injected blood into an intestinal venous segment at a constant rate. When venoconstriction took place, the initial volume in the venous segment decreased and the pressure-volume curve became flatter and more sigmoid in shape (fig. 6A).
ROSS, FRAHM, BRAUNWALD

Simultaneous recording of pressures in the venae cavae, aorta, and the two isolated carotid sinuses. As carotid sinus pressure was lowered, reflex arteriolar constriction occurred. In order to compensate for the increase of venous return and to maintain intravascular blood volume constant, it was necessary to augment systemic perfusion rate. When carotid sinus pressure was re-elevated, systemic perfusion rate was returned to the control level to keep intravascular blood volume constant.

It was postulated that with the smaller venous volume accompanying venoconstriction, the more distensible muscular elements of the vein were predominant in their effects on the major portion of the pressure-volume curve; with the larger venous volume accompanying venodilatation, the less distensible fibrous elements predominated in their effect. The initial portion of the venous pressure-volume curve of the constricted vein was found to be steeper than the remainder of the curve, resulting in a sigmoid shape; this effect was considered to result from operation of the law of Laplace. In experiments in which changes in venous volume could not be measured, the curves were plotted with their origin on the volume axis at zero, and changes in shape only could be compared (fig. 6B).

The alterations of the venous occlusion curves in the experiments reported herein suggest similar interpretations, although the exact anatomical extent of the vascular bed in which distensibility is measured by the present method is somewhat uncertain. Since arterial pressure fell whenever venodilatation occurred and rose when venoconstriction took place, the possibility was considered that these parallel alterations in arteriolar tone might influence the shape of the venous occlusion curves. Evidence against this possibility was provided by the model experiments already mentioned and the observations that a substantial diminution of intravascular volume and lengthening of the VR times took place when arteriolar dilatation occurred following acetylcholine administration.

It was observed that the effects of the vaso-
active drugs on the shape of the venous occlusion curves were similar to those reported by Alexander.\textsuperscript{23} The demonstration that large volumes of blood shifted simultaneously with these changes in the shape of the venous occlusion curves indicates that the point of origin of the curves on the volume axis was altered as well (fig. 6A).

The possible importance of reflex venomotor activity in the regulation of cardiac output is well recognized, and studies on isolated venous segments in experimental animals\textsuperscript{7-13} have demonstrated active venomotion in response to vasoactive drugs and neurogenic stimuli; however, attempts to assess the effects of these reflexes on the total venous return to the heart and on the volume of the venous bed have been few. Rashkind and associates, using the preparation previously discussed, found that the volume of blood in the venous reservoir decreased by an average of 75 ml. after stimulation of a single sinus nerve,\textsuperscript{14} but some of the problems in the interpretation of this data have already been cited. In addition, electrical stimulation of the sinus nerve simultaneously activates chemoreceptor fibers, thereby clouding deductions regarding baroreceptor function.\textsuperscript{1} Bartelstone measured outflow from and pressure in the inferior vena cava following simultaneous occlusion of the aorta and inferior vena cava.\textsuperscript{15} Carotid occlusion during this procedure resulted in an increase in outflow as well as a pressure rise in the inferior vena cava. These findings suggested that displacement of blood from peripheral veins into the occluded caval segment had occurred. The venous occlusion curves obtained in the present experiment are not strictly comparable to the circulatory occlusion curves of Bartelstone, since the latter curves spanned only the lower portion of the sigmoid venous pressure-volume curve.

In the present study, the use of general anesthesia, an open-chest, cardiopulmonary bypass, and isolation of the carotid sinuses inevitably compromised the reactivity of the preparation; nevertheless, reflex alterations in intravascular blood volume, venous return, and the venous occlusion curves were marked and attest to the importance of their influence on cardiac output.

The baroreceptor mechanism thus assumes a broader integrative role in circulatory regulation. It appears that the well-known homeostatic role of these receptors may be extended to include the reflex control of the venous bed. Thus, when hypotension activates the baroreceptor mechanism or when a sympatheo-adrenal discharge is initiated by exercise, anxiety, or other stimuli, not only are arteriolar constriction, tachycardia, and increased myocardial contractility produced, but in addition reflex vеноconstriction results in an augmentation of venous return to the heart which stimulates a further increase in the cardiac output.

**Summary**

Changes in systemic vascular volume, in venous return, and in the distensibility of the venous system were studied in an experimental canine preparation. The use of an extracorporeal circulation permitted complete exclusion of the heart and lungs and allowed continuous measurement of alterations of intravascular blood volume and of venous return to the oxygenator. Brief occlusion of the venous outflow line permitted the inscription of venous pressure-volume curves. Hypotension in the isolated carotid sinuses, the administration of catecholamines or of acetylcholine resulted in vеноconstriction, evidenced by a decrease in vascular volume, an increase in venous return, and flattening of the venous occlusion curves. Conversely, carotid sinus hypertension or the administration of trimethaphan produced venodilatation, a decline in venous return, and an increase in vascular volume. The significance of these observations in the regulation of cardiac output is discussed.

**References**


Influence of Carotid Baroreceptors and Vasoactive Drugs on Systemic Vascular Volume and Venous Distensibility

JOHN ROSS, JR., CHARLES J. FRAHM and EUGENE BRAUNWALD

With the technical assistance of Mr. Robert M. Lewis

Circ Res. 1961;9:75-82
doi: 10.1161/01.RES.9.1.75

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1961 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/9/1/75

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research 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 Research is online at:
http://circres.ahajournals.org/subscriptions/