Studies in Hemodynamics and Hypertension

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Abstract—This review covers a representative sampling of investigations in hemodynamics and hypertension performed by the author during the period from approximately 1945 to 1980. The hemodynamic studies included a description of changes associated with congestive heart failure and with acute myocardial infarction. These studies emphasized for the first time the importance of left ventricular afterload and of the mobilizable venous reservoir. Other hemodynamic studies included diverse subjects such as the first and only recordings of pulse waves in arteries as small as 200 μm in diameter, velocity differences between red blood cells and plasma, turbulent blood flow in the ascending aorta, increase in velocity of blood flow of leg veins under compression, rates of transcapillary flow of solutes in humans, and the first use of external arterial pulse wave recordings to assess vascular compliance. Pioneer studies in hypertension included the first use of an antihypertensive drug to treat malignant hypertension and the first report of the treatment of hypertension with a thiazide diuretic. (Hypertension. 2001;38:1-5.)

Key Words: hemodynamics ■ drug therapy ■ blood vessels

Several colleagues have commented that my research contributions are known solely as the chairman of the Veterans Administration Cooperative Study on the drug treatment of hypertension.1,2 Because my other contributions have been either overlooked or forgotten, they suggested that I summarize some of them for the journal of the Council for High Blood Pressure Research, Hypertension. What follows are examples of my other contributions in cardiovascular research.

Hemodynamics in Cardiac Disease

Hemodynamics of Congestive Heart Failure

Until recent times, treatment of congestive heart failure (CHF) consisted of digitalis, bed rest, and reducing congestion on the right side of the heart.3 This approach remained essentially unchanged until the late 1970s when several investigators “discovered” the therapeutic effectiveness of vasodilator drugs in relieving the signs and symptoms of CHF.4–6 Actually, the discovery had been made 30 years earlier by several investigators but was completely overlooked or forgotten. Lyons and his associates7 made the first such observation in 1947 using the ganglion-blocking drug tetraethylammonium.

In 1949, our group showed that veratrum viride reduced blood pressure (BP) and cardiac output in hypertensive patients with normal cardiac function. In hypertensive patients with CHF, however, BP reduction was accompanied by an increased cardiac output.8–10 Total peripheral resistance was significantly reduced in the heart failure patients. Patients with CHF due to causes other than hypertension (eg, coronary heart disease, valvular heart disease) also showed similar hemodynamic improvement following hexamethonium. This ganglion blocker also produced venodilatation, shifting blood volume away from the congested right side of the heart to the peripheral vessels.11 This reduced preload on the right heart and helped relieve pulmonary congestion. We stated9 that “hexamethonium interrupts a vicious circle in congestive heart failure at 2 main points: (1) by decreasing the total peripheral resistance, the work demand (afterload) on the left ventricle is decreased; and (2) by reducing the filling pressure of the right heart, the overloaded right ventricle is able to contract more effectively.” We further proposed that the increased left ventricular output contributed to the unloading of the right heart and central veins, whereas the peripheral venodilatation permitted redistribution of blood volume away from the congested thoracic area to the abdominal venous reservoirs. To explain how these various influences interact, we proposed the concept of a vicious circle in CHF (Figure 1).

Venous Reservoir and CHF

The concept of a venous reservoir under sympathetic nervous system control was advanced by our group, again using hexamethonium as a pharmacological tool.11 It is estimated that 75% of the total blood volume in the resting state is contained within venules and veins.12 Therefore, constriction or dilatation of veins would have a greater effect on changing blood volume distribution than any other part of the vasculature.
In the anesthetized dog, we substituted a constant output pump for the left ventricle. Blood was diverted from the left atrium into a reservoir and then was pumped into the aorta. The reservoir level remained constant in the resting state. When norepinephrine was injected into the circulation, however, the blood in the reservoir increased by 200 to 300 mL, representing approximately one fifth of the dog’s total blood volume. Such a large transfer of blood into the central circulation came predominantly from venoconstriction because only the veins have the capacity to supply such a large volume of blood. We suggested that this was part of the “fight or flight” response system. Although this is a helpful reaction in trauma or hemorrhage, it is harmful in CHF patients. Sympathetic blockade produced the opposite effect, resulting in a decrease in a similar volume of blood from the reservoir into the animal, indicating increased venous capacity due to venodilatation.

Hemodynamics of Myocardial Infarction

In 1952, little was known of the hemodynamic changes in myocardial infarction aside from measurements of venous pressure, arterial BP, and blood volume. Using a Hamilton densitometer at the bedside, we measured cardiac output and total peripheral resistance.

Patients with small infarcts, as judged by clinical signs and symptoms, demonstrated a normal cardiac output and total peripheral resistance. Cardiac output averaged definitely, but not markedly, below normal in the patients with moderately severe clinical manifestations of infarction. In those patients with large infarcts with signs of CHF, hypotension, or both, however, cardiac output was severely reduced and total peripheral resistance was greatly increased. We interpreted the findings in the latter patients to mean that the severely reduced stroke volume activated the sympathetic nervous system to produce venoconstriction, thereby resulting in CHF.

Hemodynamics of Blood Vessels

Blood Pressure in Very Small Arteries

Little is known about the hemodynamics of very small arteries (diameter, 200 to 1000 μm). How is the level of BP and the pulse wave changed in small arteries? At what caliber do small arteries become resistance vessels, that is, where does the steep fall in BP occur?

We measured BP in small arteries using hypodermic needles 1 to 2 mm long made from the smallest bore tubing available (<100 μm OD). The needles were attached to a Statham strain gauge, and the system was filled with degassed saline solution. Tests of the frequency response of the system indicated it was flat to 30 cycles/sec.

Small artery pressures were obtained under magnification in the dog mesentery. Compared with aortic BP, the pressure pulse in arteries as small as 100 to 200 μm in diameter displayed (1) a greater reduction in systolic than in diastolic BP, (2) a more gradual systolic upstroke, (3) moderate dampening of the dicrotic wave, and (4) absence of the small presystolic deflection (Figure 2).
The average fall in BP from the aorta to these small arteries was as follows: from aorta to 1-mm-diameter arteries, 7.5 mm Hg systolic and 5.5 mm Hg diastolic; and from aorta to 200-μm-diameter arteries, 17 mm Hg systolic and 12 mm Hg diastolic. Therefore, the resistance vessels, where the steepest drop in BP occurs, must be in arterioles <200 μm in diameter.

Raising the general BP with norepinephrine or angiotensin II caused the aorta-to–small artery pressure drop to be less than normal. On the other hand, reduction of BP with hexamethonium or by hemorrhage increased the pressure drop from the aorta to the small arteries. With severe hypotension due to hemorrhage, the pulsations in the small arteries were almost obliterated.

Velocity of Flow of Red Blood Cells Compared With That of Plasma in the Circulation
In 1949, we showed in man what had been previously demonstrated in animals: the velocity of blood cells is slightly greater than the velocity of plasma. After injecting a mixture of tagged red blood cells and plasma into the brachial artery, we collected serial samples from an antecubital vein. The obtained time-concentration curves indicated that the average velocity of the red blood cells was greater than the velocity of plasma.

Blood velocity within the blood vessels is laminar, that is, it is lowest near the vessel wall and greatest in the central stream. By Bernoulli’s law, the lateral pressure of fluid flowing in a tube is inversely proportional to the velocity of flow. Because the velocity is highest and pressure is lowest in the central stream, the blood cells are moved into the faster moving center.

Characteristics of Aortic Blood Flow
What is the character of the blood flow in the aorta? Is it laminar, turbulent, or both? To find out, we placed a thermistor at the point of a hypodermic needle. After puncturing the medial wall of the aorta, we directed the needle across the diameter of a dog aorta to the lateral wall. Cold saline was continually dripped from an intra-aortic catheter placed along the lateral wall at a point 5 cm upstream of the thermistor. By withdrawing the needle in steps, we recorded the temperature at 2-mm intervals along the diameter of the aorta from the lateral to the medial wall (Figure 3). The recordings taken at the beginning of the descending aorta showed that the temperature was lowest near the lateral wall where the cold saline was infused and increased as the thermistor was moved toward the opposite side (Figure 3). The cold saline was not being mixed, and therefore, the flow was streamlined or laminar.

In contrast, temperatures in the ascending aorta remained the same across the aortic diameter, indicating mixed or turbulent flow. Flow was turbulent in the ascending aorta because the aortic root has a narrow inlet (the valve orifice) projecting into a tube of considerably larger diameter. This configuration is known to promote a jet, causing turbulence and mixing. The flow became laminar as it passed through the arch of the aorta for 2 main reasons: peak systolic flow is markedly reduced by the large branches to the head and upper extremities, and flow tends to stabilize in a curved and gradually tapering tube.

Acceleration of Flow in Leg Veins by Local Compression
In 1946, Ochsner popularized the use of leg compression by elastic stockings as a prophylaxis against phlebothrombosis in surgical patients. His rationale was to divert more blood flow from superficial veins to deep veins and thus accelerate flow in the latter.

We measured the velocity of blood flow in leg veins directly by serial roentgenography following injection of 35% diodrast. We found marked increases in blood flow velocity in both superficial and deep veins following compression of the leg with pressures as low as 20 mm Hg. The ideal compression pressure was 20 mm Hg; higher pressures increasingly interfered with venous flow.

Transcapillary Exchange and Extravascular Circulation of Solutes and Water
We devised a method for determining the net bidirectional exchange of substances permeable to the capillary walls of the human forearm. We mixed together the intravascular dye T-1824, which binds to plasma proteins; sodium thiocyanate, which distributes in extracellular fluid; and deuterium oxide (heavy water), which enters both extracellular and intracellular spaces. The mixture was injected into the brachial artery, and serial samples were taken by free flow from an antecubital vein. Changes in the relative concentrations of the permeable substances to the concentration of the intravascular tracer permitted calculation of the extent of the initial loss and the later return of the permeable substances.

During the first few minutes of the transit curve, there was a net transcapillary loss of 50% of the thiocyanate and 90% of the heavy water. The point in the time-concentration curves...
where net loss equaled net return was called the equilibrium time.\textsuperscript{22} This averaged 111 seconds for thiocyanate compared with a mean circulation time averaging 61 seconds for T-1824. The time required for half of the net transcapillary loss of thiocyanate to return to the blood stream averaged 7.5 minutes. The larger space into which heavy water enters was indicated by the longer average equilibrium time of 130 seconds and the half-return time, which averaged twice that of thiocyanate. These results indicate that more than half of the tissue water exchanges across the capillaries several times in an hour. This great movement serves as a medium through which much of the cellular metabolism is accomplished. The turnover of the extracellular thiocyanate was even more rapid.

Studies in Hypertension

Early Drug Treatments of Hypertension

In 1947, we described for the first time the remission of some of the signs and symptoms of severe and malignant hypertension using an antihypertensive drug.\textsuperscript{23} The drug was the antimalarial agent pentaquino, given in high doses. Unfortunately, side effects were too severe to permit general use. Other drugs tested during the following 10 years included veratum viride,\textsuperscript{24} hydralazine,\textsuperscript{25} and a ganglion-blocking agent, hexamethonium.\textsuperscript{9–11} Although all of these drugs had some degree of antihypertensive activity, they also caused frequent side effects. Hexamethonium was the most effective, not only as an antihypertensive agent but also as a pharmacological tool in hemodynamic research.\textsuperscript{9,11}

Thiazide Diuretics

I was fortunate to be the first to announce the treatment of hypertension with chlorothiazide at the 1957 annual meeting of the American Heart Association.\textsuperscript{26} We found that chlorothiazide enhanced the antihypertensive action of other drugs more effectively than any other drug.\textsuperscript{27,28}

The fall in BP with chlorothiazide was associated with a reduction of approximately 25 mEq body sodium and 1 to 2 L of extracellular water, which included 15% of the plasma volume.\textsuperscript{29} This loss occurred during the first 2 to 3 days of daily drug administration. No further reduction occurred with longer continuation of chlorothiazide.

Normotensive individuals exhibited the same volume losses following chlorothiazide treatment without a reduction in BP. However, chlorothiazide changed their BP responsiveness in a direction that enhanced depressor influences and decreased pressor influences.\textsuperscript{30}

Hemodynamics of Hypertension

“Hemodynamics of Hypertension”\textsuperscript{12} was a review written in 1960 at the request of Irvine Page. It has received considerable attention over the years and is still quoted to this day. The subject had only been reviewed once before and not at all since.

Pressure Changes Under the Cuff During Korotkoff Sounds

How are the Korotkoff sounds generated? To study this question,\textsuperscript{32} we used the following method: we passed a small catheter up the brachial artery. The catheter tip could be moved to any level within the artery. A standard blood pressure cuff was wrapped around the upper arm and attached to a mercury manometer. The catheter was attached to a strain gauge for recording intra-arterial pressure. The cuff pressure was recorded. A microphone was placed over the brachial artery in the antecubital space for recording the Korotkoff sounds.

The catheter tip was first positioned 2 cm above the cuff. Intra-arterial pressure, cuff pressure, and Korotkoff sounds were recorded during cuff inflation and deflation. The catheter tip was then withdrawn 2 cm, and another recording was taken. This was repeated at further withdrawals of 2 cm until the catheter tip reached 2 cm below the cuff.

When the catheter tip was under the proximal half of the cuff, small pulsations appeared during deflation when the pressure in the cuff read $=50$ mm Hg above systolic pressure. They did not penetrate through to the lower half of the cuff. Then, just at the moment of the first Korotkoff sound and at a point 2 cm distal to the midpoint of the width of the cuff, a large arterial pulse abruptly appeared and continued during further cuff deflation. Thus, during the presystolic phase, the BP in the artery under the proximal half of the cuff was at supersystolic pressure, whereas the BP under the distal half of the cuff was at 0 mm Hg. At the time of the first sound, therefore, there was a very large and abrupt pressure drop from the proximal to the distal half of the arterial segment under the cuff, probably causing turbulence and resulting sound. The pressure gradient slowly diminished during further decompression of the cuff, but the pressure drop from the proximal to the distal portions of the arterial segment under the cuff was still considerable. For example, at 20 mm Hg above diastolic pressure, the pressure difference at end diastole averaged 48 mm Hg, enough to create Korotkoff sounds. This difference disappeared when the end diastolic pressures equalized above and below the midpoint of the cuff.

Vascular Compliance in Aging and Hypertension

One of our studies has achieved some current interest.\textsuperscript{33,34} The study involved analysis of the externally recorded arterial pulse wave for the determination of vascular compliance. We recorded both the carotid\textsuperscript{15} and the brachial arterial\textsuperscript{16} pulse waves as examples of central and peripheral pulse waves, respectively. We found changes with aging and hypertension that were consistent with a loss of arterial distensibility similar to those being described today.

Hemodynamics as a research discipline has not been very popular in recent years. Yet, it presents a fertile field for investigators especially in view of the many new developments in instrumentation and other technology. I hope that this review will provide a stimulus for further investigation in a fascinating area of cardiovascular research.

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Editor’s Note

Clearly, one of the leading investigators in the field of hypertension is Edward D. Freis. It was his unique concept in the late 1950s that introduced the first randomized, placebo-controlled, multicenter trial in cardiovascular medicine and, more specifically, with antihypertensive agents. His creation has been the forerunner of many drug trials, not only in hypertension but also in cardiovascular medicine broadly. His subtle innovations included riboflavin-tagged medications that permitted the clinician to know whether the patient was taking the medication, the use of protocol-monitoring teams, safety and ethics committees, and many others. Under his leadership, antihypertensive therapy was shown not only to be safe and efficacious but also to significantly reduce morbidity and mortality.

But few investigators today are aware of his other major contributions; his hemodynamic concepts, published in Physiological Reviews in 1960, remain a classic for all who are interested in this area of basic hypertension. He is responsible for our thinking of relieving the ventricle for pressure and volume overload, for considering the role of plasma volume as a dynamic factor in understanding effective and ineffective therapy, for the importance of large arterial mechanics in more completely understanding hemodynamics and therapy, and for the importance of transcapillary migration of intra-vascular particles in the pulmonary, renal, and peripheral circulations. Unfortunately, many of his introductions to our thinking are not cited in today’s scientific literature, but they are reflected in the remarkable scientific progress of hypertension research. For is this not the basis of all scientific progress, observations, and confirmation of hypothesis made by our investigative forebears? It is for these and many other reasons, that we have invited Ed Freis to submit the foregoing paper for peer review and publication. We hope that its review by the readers will be as meaningful and satisfying as it has been for us.

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Hypertension. 2001;38:1-5
doi: 10.1161/01.HYP.38.1.1

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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