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Sympathetic Activity, Vascular Capacitance and Long-Term Regulation of Arterial Pressure

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Keywords

sympathetic nervous system; veins; blood volume; hypertension; splanchnic

INTRODUCTION

I'm honored to have been chosen to present the 2008 Arthur C. Corcoran Memorial Lecture, because Dr. Corcoran was both a brilliant scientist and one of the founding fathers in the field of hypertension research. But I'm particularly gratified to join the list of superb scientists that have preceded me as Corcoran lecturers.

When I began studying hypertension as a postdoctoral fellow, under the tutelage of Dr. Michael Brody at the University of Iowa, I quickly acquired what turned out to be a life-long interest in the integrative aspects of cardiovascular system regulation. Because of Dr. Brody's research interests, this naturally included a focus on the sympathetic nervous system. But a major stimulus for my fascination with integrative physiology was the excitement at that time over the detailed and refined mathematical model of the circulation developed by Arthur Guyton and Thomas Coleman at the University of Mississippi [1]. It is well-known of course that the model highlights the importance of body fluid volume regulation as the key determinant of long-term arterial pressure regulation. The combined impact of these two influences—at a formative stage in my research career—led to my deep interest in the following question: "Can the sympathetic nervous system participate in long-term arterial pressure regulation within the framework of the Guyton-Coleman circulatory model?" Drs. Guyton and Coleman incorporated sympathetic regulation into their model. They emphasized the importance of non-renal sympathetic activity in determining the hemodynamic pattern of many forms of hypertension; and the potential for renal sympathetic nerve activity to affect the renal function curve (pressure-natriuresis relationship) and thereby help establish the long-term value of arterial pressure. However, they also pointed out the tendency of reflex mechanisms regulating sympathetic activity to reset and thus maintain sympathetic activity at normal levels. This would minimize the influence of sympathetic activity on regulation of arterial pressure. Evidence has accumulated over the last few decades, however, based on a variety of methods in experimental animals and humans, that sympathetic nervous system activity is chronically increased (albeit modestly) in at least a subset of hypertensive individuals[2–4]. This has led to a renewed interest in how sympathetic nervous system activity—renal and non-renal—influences the circulation in hypertension. In this review, I will discuss theoretical and

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CONFLICT OF INTEREST/DISCLOSURE
None.

experimental evidence for the importance of one non-renal effect of sympathetic activity in explaining the pathophysiology of hypertension.

MECHANISMS OF LONG-TERM CONTROL OF ARTERIAL PRESSURE BY THE SYMPATHETIC NERVOUS SYSTEM

Sympathetic nervous system activity can elevate arterial pressure by: augmenting the force and/or rate of cardiac contraction; decreasing the diameter of resistance arteries; and reducing sodium and water excretion by the kidneys. Within the conceptual framework of the Guyton-Coleman model, however, only one of these actions can exert a major effect on the *long-term* level of arterial pressure. Since pressure-natriuresis is presumed to have infinite gain over the long-term within the hierarchy of circulatory control mechanisms[5], the ability of efferent renal sympathetic nerve activity to shift the pressure-natriuresis relationship to higher pressures [6], directly or indirectly (e.g. through renin release), is of paramount importance. If this were the only physiological effect of sympathetic activation, the results would be sodium and water retention, blood volume expansion and increased arterial pressure. There is good evidence supporting an important role for renal sympathetic activity in the pathophysiology of hypertension. Renal denervation lowers resting arterial pressure and also attenuates the development of hypertension in numerous experimental models[7–9]. Furthermore, sympathetic activity at rest is quite low and is only increased ~ 50% in hypertension[4, 10]; and renal tubules and juxtaglomerular cells respond to significantly lower sympathetic firing rates than do resistance arteries[11]. Thus it is quite plausible that moderately increased sympathetic nerve activity causes hypertension by affecting renal sodium and water excretion.

Nevertheless, there are some problems with this concept. First, although the majority of published studies report an effect of renal denervation on hypertension development [7], this is not uniformly the case[12, 13]. Second, evidence linking renal sympathetic activity to *chronic* changes in sodium excretion or total circulating blood volume in hypertension also is conflicting[14–16]. Third, although expansion of total blood volume alone can increase arterial pressure and account for chronic hypertension under some circumstances[17, 18], in general there is an inverse relationship between arterial pressure and total blood volume, across the spectrum from abnormally low to abnormally high pressures[19–21].

VASCULAR CAPACITANCE AND ARTERIAL PRESSURE REGULATION

If arterial pressure is not always directly related to total blood volume, then exactly how does this volume-based control system work? Guyton and Coleman recognized that hypertension is manifested through a wide variety of distinct hemodynamic patterns, and showed clearly how changes in e. g. total peripheral resistance brought on my myogenic or local vascular control mechanisms (autoregulation), vasoconstrictor hormones or sympathetic nervous system activity could produce an elevated steady-state arterial pressure associated with normal or even low total blood volumes, as long as the pressure-natriuresis mechanism was shifted to a higher pressure level [1, 5].

Another key factor built into their model—and the focus of this review--is the “blood holding capacity” of the circulation, i.e. the vascular capacitance. Simply put, it is evident that pressure within a closed but compliant fluid containing system will be determined by both the total contained fluid volume and by the fluid-holding capacity (dimensions) of the system. Although blood is held to some extent in all parts of the cardiovascular system (heart, lung, arteries, veins, etc), approximately 70% of total blood volume is contained in systemic veins[22, 23]. This is because veins have much thinner walls and larger lumen diameters than do arteries. Therefore the compliance (Δ stored volume ÷ Δ distending pressure) and capacitance (volume at a given internal pressure) of veins (at low internal pressures) are very large relative to that of arteries (venous compliance is estimated to be 30 times greater than arterial compliance in humans [24]), i.e. overall vascular capacitance is largely determined by the structure and function of veins. There is less smooth muscle in the wall of veins than in arteries, but sufficient muscle exists in all but the very smallest veins to actively regulate wall tension and venous diameter[22, 23]. Therefore even quite modest alterations in smooth muscle tone (e.g. venoconstriction) can dramatically affect the amount of blood stored within veins.

In the Guyton-Coleman model, changes in venous capacitance (in addition to total peripheral resistance) were understood to play a part in determining the hemodynamic pattern of hypertension, including the association of high arterial pressure with low total blood volume [1, 5]. They considered vascular capacitance primarily in terms of its impact on steady-state blood flow through the circulation (venous return and cardiac output). Recently, a new synthesis has been developed that focuses on blood volume *redistribution* (driven by transient flow changes) from vascular regions of differing compliances as the most critical circulatory response to alterations in vascular capacitance. Detailed explanations of this conceptual scheme are found in the works of Tyberg[25], Brengelmann[26], and Reddi and Carpenter[27]. The ideas developed by these individuals complement the theory of Schrier[28] that also highlights the importance of blood volume distribution in cardiovascular regulation. In particular, Schrier has noted that the term “effective blood volume”, often used to explain apparently anomalous relationships between total blood volume and arterial pressure, more accurately refers to the amount of blood in the arterial circulation only. Thus, redistribution of blood from the venous to the arterial system can increase effective blood volume even when total blood volume is reduced[28].

The venous system can be considered as two compartments because its capacitance function is not invested equally in all parts of the venous circulation [24]. Relative capacitance of the three major compartments of the systemic circulation (arterial, peripheral venous and central venous) are 5, 80, and 15% of total vascular capacitance (estimated to be 175 ml/mmHg for a 70 kg human) [26]. The very compliant peripheral venous compartment—mostly composed of veins within the splanchnic region—stores the great majority (~60%) of blood in the circulation. However, it is the far smaller volume of blood (~10%) in the less compliant central venous compartment composed of the thoracic vena cava and other great veins that is especially critical to circulatory dynamics[26, 27]. A decrease in peripheral compartment capacitance affects arterial pressure because it causes venous return to transiently exceed cardiac output, thereby increasing central compartment blood volume. Volumes of blood up to 10% of total intravascular volume can be transferred into the central circulation in this fashion[29]. As central blood volume increases, cardiac filling rises and the Frank-Starling mechanism causes more blood to be ejected into the very low compliance arterial system. Of course, the precise magnitude, pattern and duration of circulatory changes caused by alterations in vascular capacitance will depend on the effectiveness of baroreflex, renal, hormonal and other counter-regulatory responses to altered blood volume in the various vascular compartments. For example, the impact of increased central compartment volume on arterial pressure likely depends on 1) the efficiency of the heart’s transfer of blood into the arterial system, 2) arterial system compliance and 3) the ways in which the kidney and arteriolar resistance vessels respond to increased arterial system filling. It is essential to note that within the framework of the Guyton-Coleman model, reduced vascular capacitance alone would be incapable of causing a sustained increase in arterial pressure unless the pressure-natriuresis relationship also was shifted to a higher pressure level. In the model, such a shift would require additional external neural or humoral influences on the kidney. Other investigators have proposed, however, that such a shift may be due simply to rapid resetting of the pressure-natriuresis relationship in response to changes in renal perfusion pressure [30–33]. Some studies, however, provide evidence against resetting of the pressure-natriuresis relationship [34]

VASCULAR CAPACITANCE AND HYPERTENSION

The hallmark hemodynamic change in established hypertension clearly is increased vascular resistance. But in human subjects with established hypertension, total systemic, and specifically venous capacitance also are reduced[35]. Decreased vascular capacitance is most marked in the veins outside the central compartment[35–37], and is particularly notable in the splanchnic circulation[38]. Central redistribution of blood volume is observed in young or borderline hypertensive patients while total blood volume is normal[37, 39–41]. In established hypertension, central blood volume is near normal but total blood volume is reduced[37, 41–43]. Very similar results (i.e. increased central but not total blood volumes) have been reported in experimental hypertension in animals[44, 45]. Thus, redistribution of circulating blood without a change in its total volume could be an important aspect of the hemodynamics of hypertension.

A helpful example of the potential impact of blood volume distribution on arterial pressure is the phenomenon of supine hypertension observed in patients with peripheral autonomic failure[46]. Although most such patients have abnormally low blood pressure while standing, ~50% develop marked hypertension when they are supine. Why do some patients exhibit supine hypertension while other do not? One obvious possible explanation is that the hypertensive patients have a higher total blood volume, perhaps because of a greater propensity of their kidneys to retain sodium and water. However, no correlation was found between total blood volume and blood pressure in these patients[46]. An alternative explanation is as follows. Blood pressure is low when the patients are upright because gravity pulls blood into the lower parts of the body, where it is stored in the highly compliant veins, particularly in the splanchnic organs. This constitutes a reduction in effective blood volume. When the patients move to the supine position, gravitational forces are negated and blood is transferred back towards the central circulation. This increases effective blood volume and arterial blood pressure. Support for this scenario is provided by the fact that three treatments—head-up tilt, nitroglycerin, and sildenafil— known to be effective in treating supine hypertension[47, 48] cause either venodilation or a redistribution of blood from central to peripheral compartments. Selective arterial vasodilators on the other hand are generally ineffective[48].

Finally, it deserves mention that redistributing blood from the central compartment to the highly compliant splanchnic vasculature (peripheral compartment) leads to a chronic reduction in arterial blood pressure in association with increased total blood volume, even in individuals with sustained hypertension. For example, portal vein ligation normalizes arterial pressure in spontaneously hypertensive rats[49]; and the onset of portal hypertension in patients with hepatic cirrhosis and essential hypertension also can produce dramatic decreases in arterial pressure[50].

SYMPATHETIC NERVOUS SYSTEM AND VASCULAR CAPACITANCE IN HYPERTENSION

Small veins and venules in the splanchnic region make up the bulk of the peripheral venous compartment and also exhibit the highest degree of active venoconstriction[51–53]. Therefore, factors regulating venomotor tone in these vessels are critical in determining active changes in capacitance. Sympathetic venoconstrictor activity is quantitatively the most important determinant of venomotor tone in splanchnic veins[54, 55] and of venomotor tone in the entire circulation[56, 57]. And like the renal tubules, veins respond to much lower frequencies of sympathetic nerve activity than do arteries[58, 59]. Therefore it seems reasonable to hypothesize that moderately increased sympathetic nervous system activity could contribute to the development of hypertension by reducing vascular capacitance. This scenario was previously proposed explicitly for human hypertension[60], and substantial supporting animal data exists

[61–63]. In the last section of this brief review I will discuss in more detail theoretical and experimental evidence supporting the importance of sympathetic control of vascular capacitance in one specific form of hypertension, i.e. angiotensin-dependent hypertension.

ANGIOTENSIN-DEPENDENT HYPERTENSION

Although there is abundant data from humans and experimental animals showing that the renin-angiotensin system participates in the development of hypertension, the precise mechanisms involved remain in dispute. A very convincing case can be made that direct actions of angiotensin II within the kidney are of particular importance[64], without any necessary contribution from actions of angiotensin II outside the kidney. Here I will marshal evidence, however, for *reduced vascular capacitance* as a plausible alternative, or possibly complementary, mechanism.

Drs. Guyton and Coleman obviously were not the only researchers that constructed a mathematical model of the circulation. Luetscher and colleagues in 1973 published a detailed computer-based mathematical model of the human circulation that particularly focused on how the renin-angiotensin system contributes to arterial pressure regulation[65]. Importantly, their model emphasized the potential for the autonomic nervous system to affect long-term blood pressure regulation. The paper included the results of impressive simulations demonstrating that the model could very accurately reproduce many features of the human circulation. What conclusions did these investigators draw about the development of renin-dependent hypertension based on their model? First, “It is not necessary to assume that blood volume is increased.” Second, “cardiac output is enhanced by adrenergic activity…and supported by increased venous return from contracted peripheral capacitance vessels.” Other attempts to explain disordered arterial pressure regulation with the use of circulatory models also have emphasized the potentially important role of changes in venous compliance or capacitance[66, 67]. Thus there is theoretical support for the notion that a sympathetically mediated reduction in vascular capacitance occurs in angiotensin-dependent hypertension.

In 1980 David Young and colleagues published an experimental analysis of the hemodynamic basis of chronic angiotensin II induced hypertension in the dog[68]. Among the many variables they measured was mean circulatory filling pressure, or MCFP. When combined with measurements of blood volume, MCFP provides a good estimate of overall circulatory capacitance or compliance, properties determined for the most part by the smooth muscle tone of veins. They concluded that, “In this form of hypertension, the increase in arterial pressure was achieved without volume expansion and cardiac output elevation, but with large initial increases in arterial and venous vascular tone.” Two years later, additional studies on angiotensin induced hypertension in the dog were published[69]. These investigators focused their attention on the quantitative relationships between segmental body fluid volumes and the hemodynamics of angiotensin induced hypertension. They concluded the following: “…about half of the rise in blood pressure during angiotensin infusion is due to increased end-diastolic volume caused by blood redistribution. About 2/3 of this increase in preload is due to redistribution from the splanchnic bed…” Therefore, experimental evidence also supports the idea that reduced vascular capacitance, particularly in the splanchnic region, participates in angiotensin-dependent hypertension.

None of the studies cited up to now, however, directly addressed the question of whether changes in vascular capacitance are a *cause* of angiotensin-dependent hypertension. Recently, Dr. Andrew King and I undertook studies to investigate changes in vascular capacitance in an experimental model of hypertension in which chronic angiotensin II infusion is combined with either normal (0.4% NaCl) or high (2.0% NaCl) dietary salt intake in the rat[70]. Vascular capacitance was determined using serial measurements of blood volume and MCFP in conscious rats. One advantage of the model is that increased sympathetic nervous system activity is evident during angiotensin II infusion in animals on high, but not normal salt intake[71]. This allows investigation of two mechanistically distinct forms of angiotensin-dependent hypertension. Hypertension is more severe in animals on the high salt diet. We found increased venoconstriction during angiotensin II infusion only in rats on the high salt diet. To investigate the mechanism of this venoconstriction, we measured acute changes in MCFP in response to ganglion blockade with hexamethonium. The magnitude of the acute fall in MCFP during ganglion blockade was unchanged during angiotensin II infusion in rats on normal salt intake, but significantly increased in rats on high salt diet. We concluded that under certain circumstances (in this case, high salt diet) sympathetically mediated venoconstriction occurs in angiotensin-dependent hypertension. The question these results do not answer, however, is: Does sympathetic venoconstriction play a part in *causing* AngII-salt hypertension?

Experiments we performed to determine if sympathetic venoconstriction caused hypertension in rats receiving high salt diet and angiotensin II infusions focused on the sympathetic innervation of the splanchnic region[72]. As discussed earlier, splanchnic veins contain a substantial fraction of the circulating blood volume; and that blood is readily mobilized into the central circulation by low plevels of sympathetic nerve activity. Splanchnic sympathetic nerve activity has been reported to be increased in angiotensin-induced hypertension in rats[73]. Finally, surgical section of the splanchnic sympathetic nerves was an early—and generally successful—treatment for hypertension in human patients[74]. The method we chose to achieve splanchnic sympathetic denervation was to remove the celiac ganglion plexus, which supplies the majority of sympathetic innervation to the splanchnic region. We confirmed the effectiveness of denervation by measuring norepinephrine content in various splanchnic organs. The main finding of our study was that sympathetic denervation of the splanchnic region significantly attenuated, but did not fully prevent, hypertension development during chronic angiotensin II infusion in rats on high salt diet. Importantly, the increased venoconstriction (presumably for the most part splanchnic) that normally occurs in this model of hypertension was abolished by splanchnic sympathetic denervation. Only a small portion of sympathetic innervation to the kidney passes through the celiac ganglion in the rat [75, 76]. But to confirm that the effect of celiac ganglionectomy was not due to removing renal sympathetic innervation, we showed that selective renal denervation alone did not attenuate hypertension development during chronic angiotensin II infusion in rats on high salt diet [72]. Another recent study in rabbits also showed no effect of renal denervation on angiotensin-induced hypertension [12]. Finally, we found that splanchnic denervation had no influence on hypertension development in rats receiving normal salt diet and angiotensin II infusion. We concluded that sympathetically mediated splanchnic venoconstriction is one, but obviously not the only, cause of hypertension in angiotensin-dependent hypertension.

PERSPECTIVES

My overall conclusions are that venous smooth muscle tone and vascular capacitance contribute to long-term blood pressure regulation; and that this is one important mechanism by which elevated sympathetic nervous system activity can lead to hypertension. One attractive aspect of this idea is its congruence with the large body of data showing a weak or even inverse relationship between total blood volume and arterial blood pressure, although additional mechanisms also can account for this phenomenon, as discussed earlier. It also helps explain some other characteristics commonly found in hypertensive individuals, such as exaggerated increases in cardiac output and natriuresis during acute volume loading. What are some additional implications?

First, because of the finite blood storing capacity of the peripheral venous compartment, blood volume redistribution can affect arterial pressure level only over a limited range of blood volumes. The gain of this pressure control mechanism, therefore, is limited, especially under conditions associated with substantial blood volume excess or deficit. Second, vascular capacitance is merely one component of a complex, interacting regulatory network, as highlighted in detailed mathematical models of the circulatory control system. One important function of capacitance regulation within that network probably is modulating the gain of other control mechanisms. For example, as noted by Guyton and colleagues, reduced vascular capacitance could markedly amplify the hemodynamic effects of renal sodium and water retention. Third, experimental and clinical findings suggest that the impact of sympathetically mediated changes in vascular capacitance may be larger during the development of hypertension than during its sustained phase. Finally, it should be noted that many factors besides the sympathetic nervous system affect venous structure and function, and thus likely participate in the regulation of vascular capacitance. Examples include endothelin, nitric oxide, reactive oxygen species, and other pro- and anti-inflammatory molecules. Capitalizing on the overall concept I’ve presented here to develop new approaches to cardiovascular therapy targeting capacitance regulation will require a more thorough understanding of all factors affecting venous structure and function.

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