The effects of hypertension on the cerebral circulation

Paulo W. Pires, Carla M. Dams Ramos, Nusrat Matin, and Anne M. Dorrance

Department of Pharmacology and Toxicology, Michigan State University, East Lansing, Michigan

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Pires PW, Dams Ramos CM, Matin N, Dorrance AM. The effects of hypertension on the cerebral circulation. Am J Physiol Heart Circ Physiol 304: H1598–H1614, 2013. First published April 12, 2013; doi:10.1152/ajpheart.00490.2012.—Maintenance of brain function depends on a constant blood supply. Deficits in cerebral blood flow are linked to cognitive decline, and they have detrimental effects on the outcome of ischemia. Hypertension causes alterations in cerebral artery structure and function that can impair blood flow, particularly during an ischemic insult or during periods of low arterial pressure. This review will focus on the historical discoveries, novel developments, and knowledge gaps in 1) hypertensive cerebral artery remodeling, 2) vascular function with emphasis on myogenic reactivity and endothelium-dependent dilation, and 3) blood-brain barrier function. Hypertensive artery remodeling results in reduction in the lumen diameter and an increase in the wall-to-lumen ratio in most cerebral arteries; this is linked to reduced blood flow postischemia and increased ischemic damage. Many factors that are increased in hypertension stimulate remodeling; these include the renin-angiotensin-aldosterone system and reactive oxygen species levels. Endothelial function, vital for endothelium-mediated dilation and regulation of myogenic reactivity, is impaired in hypertension. This is a consequence of alterations in vasodilator mechanisms involving nitric oxide, epoxyeicosatrienoic acids, and ion channels, including calcium-activated potassium channels and transient receptor potential vanilloid channel 4. Hypertension causes blood-brain barrier breakdown by mechanisms involving inflammation, oxidative stress, and vasoactive circulating molecules. This exposes neurons to cytotoxic molecules, leading to neuronal loss, cognitive decline, and impaired recovery from ischemia. As the population ages and the incidence of hypertension, stroke, and dementia increases, it is imperative that we gain a better understanding of the control of cerebral artery function in health and disease.

artery remodeling; cerebral vasculature; hypertension

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The brain is one of the most highly perfused organs in the body. Yet our knowledge and understanding of this vascular bed in health and disease lags behind that of the peripheral circulation. The cerebral vasculature has several unique features that require it to be considered separately from other vascular beds (30, 50, 67). For example, the large cerebral arteries contribute significantly to the cerebral vascular resistance and therefore contribute to the regulation of cerebral blood flow (70). Also, the cells making up the vessels interact with a diverse array of other cell types including neurons, astrocytes, pericytes, and glial cells. Finally, the presence of the blood-brain barrier (BBB) at the level of the endothelium confers unique properties on the cerebral circulation (2). Many studies have focused on the effects of hypertension on the cerebral arteries. These studies are of paramount importance because hypertension is a major risk factor for stroke (110, 120), which is a leading cause of death in the United States. Hypertension has also been implicated in vascular cognitive impairment (183) and Alzheimer’s disease (109, 185), and both of these conditions have a significant vascular pathology. The purpose of this review is to highlight recent developments in the study of the effects of hypertension on the cerebral circulation. This review will focus on three aspects of the cerebral circulation: 1) artery structure, 2) artery reactivity, and 3) BBB function. These subject areas were selected because significant knowledge gaps exist in each. Table 1 contains the definitions of commonly used terms in the field.

Cerebral Vessel Anatomy

The anatomy of the cerebral circulation was recently eloquently described in detail (30); therefore, discussion here will be limited to the intracranial arteries frequently studied in hypertension. The basilar artery, which arises from the vertebral arteries, runs along the midline of the brain stem and connects with the circle of Willis, an anastomotic ring that allows for cross perfusion of the cerebral hemispheres. Three large arteries branch off of the circle of Willis; these are the posterior, anterior, and middle cerebral arteries, with the latter being the best studied (Fig. 1A). These large cerebral arteries branch into the pial or leptomeningeal arteries, which form a
collateral network that allows cerebral blood flow to circumvent an occlusion. In fact, this is one of the first areas identified as having cerebrovascular dysfunction because of hypertension; the pial collateral arteries from stroke-prone spontaneously hypertensive rats (SHRSP) have an impaired ability to dilate in response to an ischemic insult compared with the same vessels in normotensive rats (41). This is thought to contribute to the large infarct observed after middle cerebral artery (MCA) occlusion in SHRSP (43). The large cerebral and pial arteries carry a significant amount of the vascular resistance, making them important regulators of cerebral blood flow (30, 70). Interestingly, the contribution of the different segments of the vascular bed to cerebrovascular resistance changes as hypertension develops in spontaneously hypertensive rats (SHR). In the established phase of hypertension, the small arteries and arterioles carry more of the vascular resistance than they do in young rats with developing hypertension (18). Most studies of the effects of hypertension on cerebral arteries have been conducted in young, albeit hypertensive, rats. Because the control of vascular resistance changes with the duration of hypertension, studying older hypertensive rats may yield a different, and perhaps more clinically relevant, picture of the vascular response to hypertension.

The penetrating and parenchymal arterioles enter the brain and perfuse the parenchyma (Fig. 1B). The penetrating arterioles are located in the Virchow-Robin space and are bathed with cerebrospinal fluid. The penetrating arterioles connect pial vasculature with the parenchymal arteriole capillary beds that perfuse the brain parenchyma. Unlike the surface arteries and pial arterioles, the penetrating arterioles have very few anastomoses (139). Thus the penetrating arterioles control the blood flow to very discrete regions of the cortex and act as a bottleneck to blood flow between the surface of the brain and the capillary bed (152). The parenchymal arterioles are, as their name suggests, located in the parenchyma surrounded by astrocytic end feet (37). Little is known about how hypertension affects these arteries (16, 23, 113).

The parenchymal arterioles give rise to capillaries. Capillary endothelial cells are surrounded by pericytes, and these two cell types are encased in the basal lamina. The astrocytic end feet abut against this basal lamina, and these three cell types, along with adjacent neurons, make up the neurovascular unit, a region of the cerebral vasculature that has garnered a huge amount of interest recently, largely because it has been viewed as a potential therapeutic target for ischemic strokes (50). Capillary endothelial cells are commonly used to study BBB function. It is important to note that the barrier properties of the cerebral circulation are not limited to the capillaries; the large arteries and arterioles also contribute (30, 149).

There are stark differences in the innervation of the cerebral blood vessels depending on their location in the brain (Fig. 1B). The pial arterioles receive extrinsic innervation from the peripheral nervous system. The nerves involved mostly arise from the superior cervical ganglion, although some fibers arise from the sphenopalatine, otic, and trigeminal ganglia. These nerves form a network of varicose fibers within the adventitia of the arteries. The density of these fibers begins to fall as the arteries enter the Virchow-Robin space, and they are not present in the parenchymal arterioles (83). The parenchymal arterioles receive intrinsic innervation from within the neuropil. Cortical microvessels receive noradrenergic, serotonergic, cholinergic, or GABAergic afferents from subcortical neurons from the locus coeruleus, raphe nucleus, basal forebrain, or local cortical interneurons (83), although the nerves associated with the vessels mostly target the astrocytes around the blood vessels (38). Similarly the postsynaptic receptors for neurotransmitters vary within the vascular tree. For example, norepinephrine causes submaximal contraction in the MCA through activation of the α1-adrenoreceptors (57, 92), but β-adrenoreceptors predominate in the parenchymal arterioles and they elicit dilation

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in response to norepinephrine. Similar heterogeneous expression exists for the serotonin receptors (121).

Hypertension-Associated Changes in The Structure of the Cerebral Vasculature

An increase in peripheral vascular resistance is a hallmark of hypertension. Vascular resistance can be increased by reducing the lumen diameter or the number of arteries or by increasing the length of arteries. There is ample evidence in the literature to suggest that hypertension reduces both the lumen diameter and the vessel number in the cerebral vasculature.

Vessel Rarefaction

Rarefaction or loss of arterioles and capillaries has been reported for several models of hypertension although the effects are not uniform across vessel types or models of hypertension. Sokolova et al. (188) using several models of hypertension including renal wrap, deoxycorticosterone acetate (DOCA)-salt, and SHR. In renal wrap and DOCA-salt hypertensive rats, there was a 25–50% reduction in the number of pial arteries and intracerebral capillaries (inner diameter = 1.4–5.6 μm). A reduction in the capillary number was also observed in the SHR (188). The authors did not report the effects of hypertension on pial artery numbers in SHR, but others have confirmed a reduced capillary density in these rats. In this case, the reduction in capillary density was likely blood pressure dependent as it did not occur in young SHR but had developed in 12-wk-old rats with marked hypertension (162).

Whereas hypertension reduces the number of intracerebral capillaries, the same cannot be said for the pial arteries where the effects of hypertension are more controversial, particularly in genetic models of hypertension. Coyle and Heistad (42) showed that the number of pial collateral vessels between the MCA and the anterior cerebral artery is the same in SHRSP and normotensive rats (42). This finding was confirmed by

Fig. 1. A: large cerebral arteries and the circle of Willis. B: cross-sectional representation of a segment of the cerebral circulation including the perivascular nerves. Extrinsic innervation of the vessels at the surface of the brain comes from the peripheral nervous system (PNS), nerves originate in the superior cervical (SCG), sphenopalatine (SPG), or otic (OG) or trigeminal (TG) ganglion. Arteries within the brain parenchyma, or the microcirculation, receive intrinsic innervation; these nerves originate in the central nervous system (CNS). Cortical microvessels receive norepinephrine (NA), serotonin (5-HT), acetylcholine (ACh), or GABAergic afferents from subcortical neurons from the locus coeruleus, raphe nucleus, basal forebrain, or local cortical interneurons. Inset: neurovascular unit, which consists of the vascular endothelium, and smooth muscle cells or pericytes, astroglia, and neurons. CGRP, calcitonin gene-related peptide; GABA, y-aminobutyric acid; NKA, neuropeptide Y; NPY, neuropeptide Y; PACAP, pituitary adenylate-cyclase activating polypeptide; SOM, somatostatin; SP, substance P; VIP, vasoactive intestinal polypeptide. Reproduced from Hamel (83) with permission.
Arteriole and capillary loss could lead to a reduction in cerebral blood flow, which could in turn cause chronic hypoperfusion of the brain. Although this has not been directly studied in hypertension, studies in a mouse model of cerebral small vessel disease suggest this is a possibility. In mice with small vessel disease, capillary loss in the white matter was observed before a significant reduction in cerebral blood flow and white matter injury was observed (107). Capillary loss may be the mechanism responsible for the increased risk of vascular cognitive impairment or vascular dementia in patients with hypertension (47). However, to the best of our knowledge there are no studies documenting cerebral artery rarefaction in hypertensive patients. Several unknowns remain. For example, it is not clear whether intervention in hypertensive rats reduces rarefaction or whether vessel loss can be reversed. Hopefully, the increasing use of advanced imaging techniques will answer these questions in a definitive manner.

Artery Remodeling and Hypertrophy

Hypertension results in changes in the structure of the arteries that makes them different from those of a normotensive animal or patient. The terminology to describe these structural changes has developed over a number of years. Initially, the term remodeling was used to describe a reduced lumen diameter and increased wall-to-lumen ratio (13). Remodeling can be described as inward or outward, depending on how the lumen diameter changes. Later modifications to the term remodeling took into account the fact that growth is not always part of the remodeling process. The term eutrophic remodeling is used to indicate a change in media-to-lumen or wall-to-lumen ratio without a difference in the wall cross-sectional area. Hypertrophic remodeling occurs when the wall area is increased, and hypotrophic remodeling describes a reduced wall area along with reduced wall-to-lumen ratio (146). Artery remodeling can be quantified using the remodeling index, which is the percent change in lumen diameter attributed to eutrophic remodeling, and the growth index, which is the percent change in the cross-sectional area (13, 89). Although these indexes provide important information, they are not frequently reported in the literature.

Studies to define the type of remodeling in a given vascular bed should be conducted on fully relaxed vessels. Most commonly, these studies are conducted using calcium-free solutions; some researchers also include calcium chelators and vasodilators. For the purpose of this review, measures made under these conditions will be described as the passive structure of the arteries. It is important to note that under physiological conditions, the ability of arteries to contract and dilate adds another layer to the regulation of blood flow that cannot be accounted for in studies of passive structure.

The passive structure of arteries is particularly important in situations like cerebral ischemia where the vessels around the occlusion become maximally dilated. In this situation, small changes in passive lumen diameter will dramatically affect blood flow. The increased wall-to-lumen ratio observed in arteries from hypertensive rats is generally thought to cause an increase in the vascular response to constrictor agents (145, 147, 199). However, several lines of evidence suggest that in the large cerebral arteries from SHRSP, the contractile response is reduced despite an increase in the wall-to-lumen ratio (3, 5, 201). This unexpected finding suggests that smooth muscle cells (SMCs) in cerebral arteries from hypertensive rats may compensate for artery remodeling by decreasing their responsiveness to constrictor agents.

The change in artery structure that occurs with hypertension is one of the better-studied aspects of the cerebral circulation. Folkow et al (72) first proposed in 1973 that a reduction in the lumen diameter of arteries increases vascular resistance. A recent review by Mulvany (144) highlighted the importance of vascular remodeling in the pathogenesis of hypertension. The effects of hypertension on artery structure have been reviewed in the past (9, 89, 91), and we have compiled some of the key historical findings along with more recent studies in Table 2. Although this is not an exhaustive list, it is a representative list of major findings in the field.

Cerebral artery hypertrophy and remodeling are adaptive processes that reduce the stress on the artery wall and protect the arterioles and downstream capillaries and venules from increased blood pressure (12, 117). Failure of the cerebral arteries to remodel in response to increased blood pressure has detrimental effects including vasogenic edema and BBB breakdown (95).

Hypertension increases the tangential stress on the artery wall (88). To maintain this stress within a physiological range in the face of elevated intraluminal pressure, artery wall thickness increases. In cerebral arteries this is generally associated with a reduction in the lumen diameter (89, 143) and an increase in the wall-to-lumen ratio. The latter is an important prognosticator of end-organ damage (102) and cardiovascular events such as stroke or myocardial infarction (46). The effects of hypertension on the area of the artery wall have been more difficult to define. This might be because in studies using pressurized arteries or cranial windows, this is often a derived variable, compounding experimental errors, making statistical significance more difficult to achieve. Clarifying the effect of hypertension on the wall area could help define the mechanisms responsible for artery remodeling.

Generally, in models of essential hypertension, such as the SHR and SHRSP, the large vessels like the MCA (52, 174) and pial arteries (13) have smaller lumens and thicker walls. The same can be said for the MCAs from rats with obesity-induced hypertension (49, 157), mineralocorticoid receptor-dependent hypertension (54, 156), and NE-nitro-l-arginine methyl ester (l-NAME)-dependent hypertension (140). A reduction in the lumen diameter of pial arteries has also been observed in DOCA-salt hypertensive rats (188). Interestingly, in renal hypertension, the pial arterioles have a normal lumen diameter, but the wall thickness is increased, and although not measured, this should increase the wall-to-lumen ratio (11). These studies highlight the fact that blood pressure alone is not the sole stimulus for the reduced lumen diameter found in many models.
of hypertension. In fact, the blood pressure independency of the remodeling process has proven to be a fruitful area of research as discussed below.

In SHRSP, pial artery remodeling develops as the rats age. In 3- to 4-mo-old SHRSP, the passive lumen diameter of the pial arteries is not reduced, but by 10–12 mo of age, there is a marked inward remodeling of these arteries compared with arteries from normotensive Wistar-Kyoto (WKY) rats (10, 13). It is important to note that at 3 mo of age, SHRSP are markedly hypertensive (45), so the pial arteries maintain a normal structure for some time even in the presence of elevated blood pressure. The MCAs from SHRSP have smaller lumens and an increased wall-to-lumen ratio, and this remodeling develops earlier than it does in the pial arteries (52, 168, 174). As with rarefaction, this suggests that various segments of the vascular bed remodel differently in response to hypertension. The progression of remodeling down the arterial tree to the smaller vessels over time is in keeping with the studies showing that vascular resistance increases in the smaller vessels in the sustained phase of the hypertension (18).

The structural alterations in cerebral arteries from SHRSP are accompanied by alterations in the SMC organization in the artery wall. Under normal conditions, the SMCs are arranged circularly around the artery wall. Using confocal microscopy to image pressurized basilar arteries from SHRSP, Arribas et al. (3, 5) showed a disorganization of the SMCs in the medial layer compared with arteries from normotensive WKY rats. In the SHRSP, many of the SMCs were orientated such that their long axis was no longer at a 90° angle to the direction of blood flow (3, 5). These misaligned cells were in discrete areas of the vessel wall, and were associated with a reduced thickness of the advential layer. The authors present the interesting idea that...
these areas are points of weakness in the artery that could increase the risk of hemorrhage in SHRSP (3). The changes in the organization of the medial layer were associated with impaired contraction to potassium chloride. The same group of researchers also studied rats with experimental hypertension induced by nitric oxide (NO) synthase inhibition with L-NAME. Whereas artery remodeling was observed in these rats, the authors did not observe the same disorganization of the SMCs (4). It is therefore possible that this cell reorientation is a genetic trait particular to the SHRSP. However, it is also possible that the duration or magnitude of the hypertension contributes to the disparity in the results since the rats were only treated with L-NAME for 3 wk, whereas the SHRSP were 14 wk old when they were studied and would have had significant hypertension for at least 6 wk (45).

Effects of the Renin-Angiotensin-Aldosterone System on Artery Structure

Although the hemodynamic effects of hypertension are undoubtedly an important trigger of remodeling, studies suggest that circulating factors known to be elevated in hypertensive subjects play a major role in the process independent of blood pressure. The renin-angiotensin-aldosterone system (RAAS) has been well studied in this regard. Many studies have been conducted using angiotensin-converting enzyme inhibitors (ACEIs) (36, 82) or angiotensin receptor blockers (27, 60). These studies compared the effects of RAAS inhibition with blood pressure lowering by RAAS-independent means using β-blockers. The take home message from these studies is that blood pressure lowering alone is not sufficient to improve pial artery (27, 82) or MCA structure (116, 212) in SHR or SHRSP. β-Blockers do not improve artery structure, yet they reduce plasma renin activity and angiotensin-II (ANG II) levels (17). It is not clear why β-blockers and ACEIs do not have similar effects on artery structure because both reduce ANG II and lower blood pressure. A role for ANG II in cerebral artery remodeling is supported by studies using angiotensinogen knockout mice. The internal diameter of the anterior cerebral artery-MCA anastomoses is increased in the knockout mice compared with wild-type mice, but there was no difference in the number of anastomoses. It is possible that the lower blood pressure observed in the knockout mice affected artery structure (127).

Of particular note is a study documenting a reduction in wall thickness and wall-to-lumen ratio in aged SHR with ACEIs. In this study, rats began the captopril treatment at 12 mo of age and were studied at 15 mo. Thus the rats began treatment when they were already hypertensive and when vascular remodeling would be present. Therefore, the hypertension-induced remodeling in the pial arteries appears to be reversible (59). The same researchers recently demonstrated that low doses of ACEIs (ramipril) and angiotensin receptor blockers (telmisartan) in combination are effective at improving pial artery structure and function in young SHR. The same doses of these drugs given alone had essentially no effects on pial arteries (61). It is also worth noting that the combination therapy was not any more effective than a higher dose of either drug used alone (60). In both cases the therapies that improved artery structure also significantly reduced blood pressure. Although many of the studies described above assessed blood flow and found it to be improved (59–61), it remains to be seen whether these structural changes improve blood flow after an insult like cerebral ischemia. One thing lacking in these studies is a mechanism by which the artery structure changes and this is the next important step to take, as there may be more efficacious therapeutic candidates.

Our laboratory has taken the analysis of the effect of RAAS on cerebral arteries a step further by investigating the effects of aldosterone and activation of its receptor, the mineralocorticoid receptor, on cerebral artery remodeling. Treatment of SHRSP from 6–12 wk of age with spironolactone, a mineralocorticoid receptor antagonist, prevents the reduction in lumen diameter and increase in wall-to-lumen ratio in the MCA associated with elevated blood pressure (174). Spironolactone also increases the MCA lumen diameter in rats with established hypertension and remodeling (173). Importantly, in both studies the beneficial effects of mineralocorticoid receptor antagonism occurred without reducing blood pressure. Conversely, mineralocorticoid receptor activation with DOCA or 11-β-hydroxysteroid dehydrogenase inhibition in normotensive rats leads to MCA remodeling including increased wall-to-lumen ratio and reduced lumen diameter (54, 156). In both of these studies there was a mild to moderate increase in systolic blood pressure and a marked increase in the damage caused by cerebral ischemia induced by MCA occlusion. We have yet to elucidate whether the effects of ANG II and aldosterone are dependent on each other or additive. However, the lack of an effect of mineralocorticoid receptor antagonism on blood pressure suggests that the mechanisms responsible for the effects of aldosterone on the cerebral arteries differ from those mediated by ANG II.

Many intracellular signaling cascades activated by the RAAS could stimulate artery remodeling. ANG II and aldosterone have been linked to the production of reactive oxygen species (ROS), particularly superoxide, through NADPH-oxidase induction (171, 198). Superoxide has been implicated in the remodeling of peripheral resistance arteries (165) and coronary arteries (19) in hypertensive rats. In fact, treatment of SHRSP with the membrane permeable superoxide dismutase (SOD)-mimetic Tempol prevented the reduction in the MCA lumen diameter normally observed in SHRSP (167). For artery remodeling to occur, the extracellular matrix needs to be degraded and reorganized to allow for the movement of SMCs within the wall. The matrix metalloproteinase (MMP) family of enzymes appears to be responsible for this process (73), and MMP expression is modulated by RAAS activation. Mineralocorticoid receptor antagonist reduces MMP-13 mRNA expression in large cerebral arteries from SHRSP (173). Moreover, treatment of SHRSP with the nonspecific MMP inhibitor doxycycline increases the lumen diameter and reduces the wall-to-lumen ratio in MCAs from 12-wk-old SHRSP. These changes in structure occurred without lowering arterial pressure. Doxycycline treatment also reduced the amount of damage produced by MCA occlusion with reperfusion, and increased pial artery blood flow post-stroke as measured with scanning laser Doppler (168). In this study the doxycycline treatment was removed several days before the induction of cerebral ischemia. Therefore, the reduction in infarct size was not likely a response to acute MMP inhibition at the time of the stroke. We do not know whether Tempol or doxycycline affect the pial, penetrating, or parenchymal arterioles in hypertensive rats.
Non-RAAS-Dependent Mechanisms of Cerebral Artery Remodeling

There is a growing body of evidence suggesting that other mechanisms also contribute to hypertensive cerebral artery remodeling. Peroxisome proliferator-activated receptor-γ activation with rosiglitazone prevented inward remodeling of the posterior cerebral artery (PCA) in t-NAME hypertensive rats. In this study, mean arterial pressure was already increased by t-NAME before the rosiglitazone treatment began, and rosiglitazone had no effect on blood pressure (31). Similarly, treatment of New Zealand Zealand hypertensive rats with pioglitazone reduced media thickness of the basilar artery; in this study blood pressure was reduced by pioglitazone (119). 3-Hydroxy-3-methylglutaryl-CoA reductase inhibitors (statins) also have the potential to prevent hypertensive cerebral artery remodeling. Simvastatin reduced the wall thickness and increased the lumen diameter of the basilar artery in genetically hypertensive rats (118) and in the 2K2C hypertensive rat (125). In both these studies simvastatin lowered the blood pressure. Thus it is not clear whether the prevention of hypertension induced remodeling is a direct effect of the statin therapy or a response to the lower blood pressure.

Chloride Channels and Cerebral Artery Remodeling

Hypertrophic remodeling involves an increase in the mass of the artery wall. This can be the result of SMC hypertrophy where the cell volume increases, or it can be the result of hyperplasia or SMC proliferation. Both situations require changes in cell volume, which is tightly controlled by membrane transport processes that regulate the gain or loss of ions, such as Na⁺, K⁺, and Cl⁻ or small organic osmolytes including amino acids, polyols, and methylamines (192). The following paragraphs discuss the importance of two Cl⁻ channels in cerebral artery remodeling. It should be recognized that several other ion channels have been implicated in the cerebral artery remodeling process, including receptor- and store-operated Ca²⁺ channels (22), transient receptor potential (TRP) channels (99), large-conductance Ca²⁺-activated K⁺ channels (BKCa), and voltage-gated K⁺ channels (211). We have chosen to focus on Cl⁻ channels because this is an area that is somewhat controversial.

The volume-regulated Cl⁻ channel (I_{Cl,vol}), appears to be a key regulator of artery remodeling. Activation of this channel has been implicated in the control of SMC volume, proliferation, and apoptosis (80). The exact identity of the I_{Cl,vol} channel is not clear, but CIC-3, a voltage-gated Cl⁻ channel, is considered a prime candidate in vascular SMCs (80, 216). Blockers of I_{Cl,vol} hyperpolarize rat cerebral artery SMCs, and this results in dilation (151). Therefore, activation of I_{Cl,vol} appears to cause SMC depolarization and artery constriction. In basilar arteries from 2K2C rats, SMC hypertrophy is observed, and this increased cell size results in an increased medial area. Cultured SMCs from these arteries show a blood-pressure-dependent increase in I_{Cl,vol} activity when placed in a hypotonic solution, and this increased activity requires protein tyrosine kinase activation (180). Treatment of 2K2C rats with simvastatin reduces the activity of this channel, and simvastatin attenuates basilar artery remodeling (125). It is also possible that the contribution of these channels to hypertensive remodeling is through depolarization-induced opening of voltage-gated Ca²⁺ channels, leading to an increase in intracellular calcium and activation of Ca²⁺-dependent SMC proliferation (44, 169). This hypothesis remains untested. It is also unclear whether the changes in the activity of the Cl⁻ channels are a cause or an effect of hypertensive artery remodeling. However, the CIC-3 may be particularly important in hypertension because it is activated by many factors that are known to be elevated in, or associated with, hypertension including ANG II, endothelin-1, and ROS (55).

Other studies suggest that Ca²⁺-activated Cl⁻ channels are involved in the hypertensive remodeling process. As with the I_{Cl,vol}, the molecular identity of Ca²⁺-activated Cl⁻ channels has been difficult to define. Wang et al. (206) used the 2K2C rats to test the involvement of the TMEM16 family of transmembrane proteins in the regulation of the Ca²⁺-activated Cl⁻ current with a particular focus on TMEM16A. Interestingly, the activity of the channel and therefore the Ca²⁺-activated Cl⁻ current is reduced in SMCs from hypertensive arteries compared with arteries from control rats. ANG II reduced TMEM16A expression, and overexpressing TMEM16A reduced ANG II-stimulated SMC proliferation (206). The authors of this study proposed that the TMEM family proteins are potential therapeutic targets for vascular disease.

Cerebral Artery Autoregulation

As mentioned above, cerebral blood flow is controlled by several factors. In hypertensive patients, the remodeling process functions to normalize, or partially reduce, blood flow in the face of increased blood pressure by increasing vascular resistance (104, 111). Whereas many studies suggest resting blood flow is relatively normal in hypertensive individuals, there is some evidence that in older hypertensive patients, blood flow is reduced in specific brain regions including the occipitotemporal and prefrontal cortex and the hippocampus (15). Hypertension also impairs functional hyperemia (104), which is the increase in blood flow to regions of increased neuronal activity. Functional hyperemia requires the release of vasoactive agents from neurons, astrocytes, and the vessels themselves to cause local dilation in the parenchymal arterioles and the upstream pial arteries (95). Hypertensive patients with poorly controlled blood pressure have a decline in total cerebral blood flow as they age. This occurs independent of atherosclerosis (142) and may be a consequence of impaired cerebral artery structure and function. Hypertension also increases the lower limit of autoregulation, and this can severely impact the outcome of cerebral ischemia and the regulation of cerebral blood flow during periods of hypotension. This will be discussed in more detail below.

Cerebral Artery Function in Hypertension

The hemodynamic effects of vascular remodeling are several-fold. In hypertensive patients, the remodeling process functions to normalize, or partially reduce, blood flow in the face of increased blood pressure by increasing vascular resistance (104, 111). Whereas many studies suggest resting blood flow is relatively normal in hypertensive individuals, there is some evidence that in older hypertensive patients, blood flow is reduced in specific brain regions including the occipitotemporal and prefrontal cortex and the hippocampus (15). Hypertension also impairs functional hyperemia (104), which is the increase in blood flow to regions of increased neuronal activity. Functional hyperemia requires the release of vasoactive agents from neurons, astrocytes, and the vessels themselves to cause local dilation in the parenchymal arterioles and the upstream pial arteries (95). Hypertensive patients with poorly controlled blood pressure have a decline in total cerebral blood flow as they age. This occurs independent of atherosclerosis (142) and may be a consequence of impaired cerebral artery structure and function. Hypertension also increases the lower limit of autoregulation, and this can severely impact the outcome of cerebral ischemia and the regulation of cerebral blood flow during periods of hypotension. This will be discussed in more detail below.
constant levels over a wide range of arterial pressures; this occurs through the mechanism of autoregulation. In most adult humans autoregulation operates between mean arterial pressures of 60 and 150 mmHg (166). When the cerebral perfusion pressure rises above or falls below the autoregulatory range, the control of flow is lost and flow becomes dependent on mean arterial pressure (158). Pressures above the autoregulatory range cause increases in blood flow followed by vasogenic edema. Conversely, pressures below the autoregulatory range result in low perfusion of the brain and subsequent ischemic injury (30). Several mechanisms have been proposed to contribute to the control of autoregulation in the cerebral circulation. These include neuronal NO production (56, 106, 166, 195) and metabolic by-products (166). The sympathetic and parasympathetic nervous systems were not thought to be involved in cerebral blood flow autoregulation (21); however, recent studies in humans have suggested a role for both dynamic sympathetic vasoconstriction (84) and cholinergic vasodilation (85) in the control of cerebral autoregulation. Blood flow itself also plays a role in autoregulation, and this concept was recently reviewed by Koller and Toth (115). This review describes the evidence that flow can induce contraction or dilation in the cerebral vasculature dependent on the artery studied. For example, the basilar artery dilates in response to increased flow, whereas the MCA constricts.

Myogenic Reactivity

The myogenic activity of the cerebral arteries also plays an important role in cerebral blood flow autoregulation. Myogenic reactivity is the ability of the artery to change its tone to respond to fluctuations in intraluminal pressure while keeping blood flow constant as first described by Bayliss in 1902 (14). This is particularly important at higher pressures when the arteries constrict to maintain blood flow at a constant level (Fig. 2) (158). Basal vascular tone contributes to cerebrovascular resistance, and much of this tone is thought to be myogenic in nature (68). Cerebral arteries from normotensive rats maintain myogenic reactivity over a range of intraluminal pressures from about 60 to 140 mmHg. The myogenic response is an intrinsic property of SMC to stretch that is in part controlled by 20-HETE production (75). The extent and duration of the response is modulated by the endothelium and removing the endothelium increases myogenic tone (35, 74). The endothelium modulates myogenic reactivity through many mechanisms, several of which are impaired in other vascular beds in subjects with hypertension (137). NO (69), prostacyclin (128), and endothelium-derived hyperpolarizing factor (EDHF) (78) are all released from the endothelium and have the ability to reduce myogenic constriction. Conversely, 20-HETE production is increased in cerebral vessels from hypertensive rats, and this could increase the myogenic tone (58).

Myogenic responses are frequently studied ex vivo using pressure myograph systems that allow the responses of the artery to pressure and stretch to be studied without the confounding effects of circulating factors or metabolites. Oso et al. (158) have described in vitro myogenic behavior of the PCA as occurring in three phases. Phase 1 is the development of tone that occurs at intraluminal pressures of 40–60 mmHg and involves SMC depolarization, increases in intracellular calcium, and reductions in vessel tension and tangential stress. Phase 2 is described as myogenic reactivity that occurs between 60 and 140 mmHg intraluminal pressure. In this phase, the tone developed in phase 1 is maintained despite the increase in wall tension and intraluminal pressure. Finally, phase 3 is force-mediated dilation. This occurs when the intraluminal pressure increases to a level where tangential wall stress exceeds the ability of SMCs to contract and generate active wall stress to oppose the pressure-induced stress, resulting in forced dilation (158).

Despite the potential importance of studying autoregulation and myogenic reactivity in models of hypertension, the available studies are limited and conflicting. Pressure myograph studies have shown that PCAs from normotensive WKY rats exhibit myogenic reactivity over a range of intraluminal pressures from ~40 to 150 mmHg, after which force-mediated dilation occurs. In SHR, myogenic reactivity occurs over a higher range of pressures from ~65 to 190 mmHg (159). Another study showed that myogenic tone generated over a wide range of intraluminal pressures is increased in PCAs from SHR compared with WKY rats. However, the pressure at which force-mediated dilation occurs was the same in both strains (103). MCAs from male SHRS-fed regular chow show similar myogenic responses to WKY rats. Interestingly, the SHRSP females, which have lower pressure than males, exhibited relatively more myogenic constriction than female WKY rats (96). When fed a high-salt diet, MCA from SHRSP lose their ability to constrict in response to increasing intraluminal pressure (101). Consequently, the downstream arterioles and capillaries will be exposed to higher pressures and increased flow, increasing the probability of a cerebral hemorrhage and edema. In fact, SHRSP fed a high-salt diet from weaning have an almost complete loss of autoregulation at 13 wk of age, the age at which they start to develop hemorrhagic strokes. The loss of autoregulation is accompanied by a pressure-dependent increase in cerebral blood flow (186), suggesting the high intraluminal pressure is transferred to downstream arterioles. The mechanism responsible for the loss of regulation in the salt-loaded SHRSP has not been identified, although the potential exists that this is a physical response to the increased blood pressure. The administration of a high-salt diet to SHRSP increases their blood pressure by 10 to 20 mmHg compared with control chow-fed SHRSP (79, 100).

Fig. 2. Cerebral blood flow in relation to artery lumen diameter. Dotted lines represent the lower and upper limits of cerebral blood flow autoregulation. Red circles represent the cerebral arteries, and blue line represents the cerebral blood flow. Modified from Mangat (129); used with permission.
Most studies of autoregulation have focused on the upper end of the autoregulatory curve. However, we may be missing important physiological effects by not considering the low-pressure end of the curve, which is referred to as the lower limit of cerebral blood flow regulation. This is the pressure below which blood flow becomes dependent on blood pressure. In this situation the autoregulatory mechanisms cannot produce further dilation and the arteries begin to collapse because the intraluminal pressure is low. This causes blood flow to fall (Fig. 2). The lower limit of autoregulation is increased in animal models and patients with hypertension (6). In SHR and in rats with renal hypertension normalizing blood pressure with ACEIs reduces the lower limit of cerebral blood flow regulation (7, 59, 204). Improving the lower limit of blood flow regulation could be important in situations like cerebral ischemia. During occlusion of a major blood vessel, the intraluminal pressure in arteries downstream from the occlusion drops and normally induces vasodilation. However, if the pressure drops below the lower limit of blood flow regulation, the diameter of the artery will be exclusively dependent on its passive diameter. Because arteries from hypertensive subjects have smaller passive diameters, this can further compromise perfusion and increase hypoxic areas.

**Endothelial Mechanisms that Regulate Cerebral Vessel Tone: NO-Dependent Mechanisms**

The best described mechanism for endothelial regulation of vascular tone is NO (Fig. 3). The enzyme endothelial NO synthase (eNOS) is the most important source of NO in cerebral arteries, and eNOS expression is reduced in cerebral microvessels from SHR compared with WKY rats (212). This impairs endothelium-dependent dilation, which could be detrimental to the outcome of ischemia because maximal dilation of the collateral vessels is required to circumvent an occlusion and minimize hypoxia and neuronal death (40). In support of this hypothesis, eNOS knockout mice have impaired cerebral perfusion following MCA occlusion, and this increases the ischemic damage (93). Some therapeutic agents have been shown to improve the outcome of MCA occlusion through...
pleiotropic mechanisms that increase eNOS activity. Such is the case for cilostazol, a phosphodiesterase-3 inhibitor and antiplatelet medication. In SHR, cilostazol increased phosphor-ylated eNOS (active eNOS) levels in the brain, and this was associated with increased cerebral blood flow after ischemia and reduced infarct size (160). Similarly, in SHRSP fed a high-fat diet, cilostazol prevented the reduction in cerebral blood flow observed in untreated SHRSP or SHRSP treated with aspirin or clopidogrel. This suggests that the effects of cilostazol are not related to its antiplatelet activity (155) and that cilostazol may improve endothelial function in SHRSP. This is clinically relevant, as recently evidenced by the Cilosta-zol Stroke Prevention Study showing that cilostazol is effective in preventing secondary ischemic strokes in patients independent from its effects on platelet aggregation (181).

NO-dependent dilation is also impaired by oxidative stress that is elevated in hypertensive arteries (197). Under physiological circumstances, superoxide is dismutated into hydrogen peroxide in a reaction catalyzed by SOD. However, excessive superoxide production might saturate the SOD defenses, leaving superoxide to react with NO and reduce the NO availability in the cerebral arteries, leading to impaired endothelial function (164). Interestingly, in normotensive rats, superoxide production in cerebral arteries is twofold higher than in peripheral arteries (138). This is in agreement with a paradoxical effect of ROS in pial arteries, where hydrogen peroxide acts as a vasodilator by activating BKCa (187). However, the effects of hydrogen peroxide on the cerebral vasculature vary with the artery studied. Hydrogen peroxide causes MCA constriction by opening L-type Ca2+ channels (24). Surprisingly, superoxide is not detected in the basilar artery of SHR under physiological conditions. This could be a consequence of SOD overexpression, because SOD inhibition raised superoxide levels above the detection limit (163). SOD may be overexpressed in response to the excessive production of superoxide and may provide an alternative vasodilator mechanism after a chronic depletion in NO (Fig. 3).

Endothelial Mechanisms that Regulate Cerebral Vessel Tone: NO-Independent Dilation

Endothelium-dependent dilation in cerebral arteries has a component which is NO and prostacyclin independent. This mechanism of dilation is referred to as EDHF (Fig. 3) (20). The exact identity of EDHF is under debate, but calcium-activated K+ channels, particularly the small- and intermediate-conduc-tance Ca2+-activated K+ channels (SKCa and IKCa, respectively), appear to be involved (191). Deletion of IKCa in mice leads to systemic hypertension and impairment of acetylcho-line dilation in carotid arteries (182). In the MCA, a large component of EDHF vasodilation depends on IKCa (131), but it is still unclear whether protein levels of IKCa are decreased in cerebral arteries of hypertensive subjects. Importantly, IKCa expression is increased in mesenteric resistance arteries from SHRSP, but EDHF dilation is impaired (76), suggesting that loss of IKCa channel expression is not sufficient to explain EDHF-impairment.

A role for TRP channels in the control of cerebral artery endothelial function has recently emerged (Fig. 3). This is one of the most exciting and rapidly evolving areas of cerebral vascular research. The TRP superfamily of cation channels comprises 28 channels divided into 6 families. These channels are non-selective for cations, and different channels subtypes have differential selectivity for monovalent or divalent cations, although they will conduct both [for a review of TRP channel biology, see the following articles (63, 203)]. TRPC3 is found in cerebral arteries and mediates vasoconstriction (172). Its expression is increased in carotid arteries from SHR, and this is linked to augmented contractility (154). To date, no one has assessed whether TRPC3 expression is increased in cerebral arteries.

The TRP vanilloid 4 (TRPV4) channel is activated by epoxycosatrienoic acids (EETs) and contributes to cerebral artery endothelium-dependent dilation (62, 64). The mechanisms of TRPV4 hyperpolarization differ between vascular SMCs and endothelial cells. In vascular SMCs, TRPV4 channels form a novel signaling complex with ryanodine receptors (RyRs) and BKCa (64). Upon opening, TRPV4 channels allow for a small Ca2+ influx that opens RyRs on the sarcoplasmic reticulum, generating a transient and localized increase in Ca2+, known as calcium sparks. These calcium sparks increase BKCa opening leading to K+ efflux and hyperpolarization (64). In endothelial cells of mesenteric resistance arteries, activation of muscarinic receptors increases the opening of a small number of TRPV4 channels, generating a calcium sparklet, which are transient increases in intracellular calcium at the mouth of a single channel (25). This calcium sparklet activates IKCa and SKCa in the endothelial cells, leading to hyperpolarization that is transmitted to the SMCs via gap junctions (189). It is important to note that calcium sparklets also occur in SMCs but are not mediated by TRPV4. TRPV4 knockdown does not cause hypertension, but it exacerbates L-NAME-induced hypertension and is linked to impairment in endothelium-dependent dilation in peripheral arteries (65). Interestingly, ROS can activate Ca2+ sparks in cerebral arteries, coupling this signal to RyRs and BKCa (210), potentially through TRPV4 activation. Despite the importance of TRPV4 in regulating endothelial function in cerebral arteries, it is unknown whether their expression and function is altered in the cerebral vasculature of hypertensive subjects.

As described above, functional hyperemia causes local dilation in the parenchymal arterioles and the upstream pial arteries (95). In parenchymal arterioles, vasodilation is a consequence of paracrine release of vasodilators such as EETs from perivascular astrocytes (86) and neurons (97). Functional hyperemia is impaired in rats with ANG-II hypertension (77) and in untreated hypertensive humans (104). Although the mechanisms regulating functional hyperemia are not fully understood, it is dependent on NO (51, 122), cyclooxygenase-2 metabolites (153), and, more importantly, EETs (176). EETs are synthesized from arachidonic acid by cytochrome P-450 enzymes and metabolized into inactive compounds by soluble epoxide hydrolase (Fig. 3) (214). EETs act directly on SMCs to cause vasodilation, through an undefined mechanism. One possibility is direct activation of TRPV4 channels by EETs (64, 205). TRPV4 activation leads to Ca2+ spark formation that leads to BKCa activation and dilation as described above (64). Inhibition or deletion of soluble epoxide hydrolase reduces blood pressure in many models of hypertension, including ANG-II hypertension (98), 2K1C (190), and DOCA-salt (130). Soluble epoxide hydrolase inhibition does not lower blood pressure in SHRSP, but it does reduce ischemic damage after MCA occlusion (53). This appears to occur through a combi-
nation of vascular and neuroprotective effects (53, 184). Although cerebral perfusion was not evaluated in those studies, it is possible that soluble epoxide hydrolase inhibition caused an increase in EET availability to the cerebral vasculature after ischemia, leading to augmentation in collateral blood flow to the ischemic penumbra and reduction in hypoxic neuronal death. In agreement with this possibility is the observation that cerebral arteries from SHR have decreased production of 11,12-EET (58). 20-HETE, another arachidonic acid metabolite, causes cerebral artery contraction. The increased NO production observed in functional hyperemia reduces 20-HETE synthesis or signaling, and this allows the EET-dependent dilation to be apparent (124).

Hypertension and BBB Function

The structure and function of the BBB has been eloquently reviewed (2). In our introduction we described the basic architecture of the cerebral microvessels where most studies of BBB function have been conducted. It is important to note that the BBB is not limited to the small vessels. The endothelial cells in the pial, penetrating, and parenchymal arteries also exhibit BBB properties (1, 175, 217), although BBB function is not frequently studied in these arteries. The BBB is a selectively permeable physical and biochemical barrier that maintains central nervous system homeostasis. The permeability properties of the BBB are derived from the composition of the neurovascular unit. The capillaries are lined by specialized endothelial cells that express transmembrane tight junction proteins including the claudins and occludins. Although most studies of the BBB focus on the endothelial cells, it should be noted that pericytes (123, 178, 202) and astrocytes (66) play key roles in barrier maintenance. We know little about how hypertension affects the contribution of astrocytes and pericytes to BBB function. It is possible that hypertension increases the number of pericytes, this was found to be the case in kidney from SHR (8).

Hypertension enhances BBB permeability and impairs its ability to regulate central nervous system homeostasis (90, 135, 161). Studies using SHRSP reveal that with chronic hypertension, there is evidence of intrinsic leakiness of the barrier that, in the absence of ischemia and hemorrhage, results in edema (196). The increased BBB permeability associated with hypertension is attenuated by ACE inhibition (150). In rats with renal hypertension, enalapril significantly reduced cortical BBB permeability and macrophage infiltration into arterioles. In this study, enalapril treatment begun after the hypertension was developed did not completely ameliorate the increase in blood pressure (150). Vascular remodeling that occurs in response to hypertension (described above) could also contribute to BBB breakdown (148). It should be noted the blood pressure was extremely high (220 mmHg systolic pressure) in the rats exhibiting the most marked BBB disruption, and therefore the potential exists that the damage to the BBB is purely a physical insult. However, the idea that artery remodeling contributes to BBB breakdown has some merit. During the remodeling process, arterial structure becomes more dynamic than when it is under normal physiological conditions, and in some cases the lumen becomes smaller, which requires rearrangement of the endothelial cells and therefore tight junction disruption. Paradoxically, the BBB in chronically hypertensive animals is more resistant to acute increases in blood pressure, possibly due to the protective effect of adaptive changes in the structure of the BBB (141). Although no studies have directly assessed why hypertension protects the BBB from acute changes in pressure, recent studies suggest that sheer stress may be involved. Preconditioning aortic endothelial cells to fluctuations in shear stress leads to a transient increase in membrane permeability, but it also promotes the expression of anti-inflammatory and antioxidant genes (81, 94, 215). This adaptive response could contribute to the resistance of chronically hypertensive animals to acute hypertension-mediated disruption of BBB.

There are few studies describing the mechanisms by which chronic hypertension increases BBB permeability but ROS and inflammation are potential mediators of hypertension-induced BBB breakdown (132, 193). Increased ROS production has several consequences in the vasculature including endothelial cell dysfunction, which can lead to increased BBB permeability (200, 209). An in vitro study in which human umbilical vein endothelial cells were treated with hydrogen peroxide indicated that oxidative stress causes reorganization of tight junctions (112). A recent study of the effects of peripheral inflammatory pain induced by A-carrageenan injection into the paw on BBB permeability demonstrated that the ROS scavenger Tempol reduced the disruption of tight junctions and attenuated the damage caused by the inflammation (126). In another study, the ROS generating enzyme NADPH oxidase was shown to partially mediate BBB disruption after experimental stroke. In this study, NADPH oxidase knockout mice had reduced BBB permeability after MCA occlusion compared with wild-type mice (108).

Clinical and experimental studies have shown that hypertension increases circulating levels of inflammatory cytokines such as tumor necrosis factor-α, interleukin 6, monocyte chemoattractant protein 1, and intercellular adhesion molecule-1 in the vasculature (71, 179, 218). Several studies show that inflammation can induce BBB opening. A study examining the effects of microglia on the BBB reported that endothelial cells cocultured with microglia are more susceptible to changes in the environment like glucose deprivation and ischemia (213). The same study showed that in vivo, mice treated with the anti-inflammatory agent minocycline had reduced BBB permeability and reduced infarct volume after stroke (213). Minocycline also inhibits MMP activity and which could reduce BBB breakdown. Similarly, systemic inflammation worsens BBB injury leading to edema in an experimental model of stroke (48).

Conclusions and Outstanding Questions

Hypertension has detrimental effects on the cerebral vasculature, which include changes in the structure and function of the arteries. There are, however, several gaps in our knowledge. Most studies conducted thus far have used relatively young, predominantly male rats or mice, yet cerebrovascular dysfunction primarily occurs in diseases of the elderly. We have learned much about how to prevent cerebrovascular disease, but we know much less about how to reverse it. There is also a need to consider hypertension effects on the cerebrovascular response to ischemia. Myogenic tone and reactivity in cerebral arteries fall with increasing durations of ischemia (33), and endothelium-dependent dilation is impaired
soon after the onset of ischemia (134, 177). Several studies indicate that during transient MCA occlusion the nonischemic MCA experiences vascular dysfunction (32–34, 105). Other studies indicate that dilation of the basilar artery is impaired post-stroke (39). Impaired artery function post-stroke also extends to the mesenteric arterial bed in the periphery (133). We do not know how the structural changes that occur with hypertension affect the vascular response to ischemia. We also do yet know the effects of sex and age on the vascular responses to an ischemic insult. Studies using a global forebrain ischemia model suggest that estrogen prevents the impaired dilation normally observed in pial arteries after induction of ischemia (170, 207). It is not clear whether this protection remains in hypertensive rats.

Not only do the cerebral vessels play a critical role in the outcome of ischemia, it is also becoming clear that vascular dementia and cognitive decline are important clinical problems that have a vascular basis. SHRSP have proven to be useful models to study vascular dementia. These rats develop many of the histopathological lesions also observed in humans with vascular dementia, such as multiple lacunar infarcts, cerebral atrophy and neuronal loss from cognitive regions of the cortex (114). It is possible that these lesions in SHRSP are due to declines in cerebral perfusion, since this correlation was recently observed in humans (136). As our population ages the incidence of stroke and vascular dementia will most probably increase highlighting the need to define ways to prevent or reverse the effects of hypertension on the vasculature. These studies will require that penetrating and parenchymal arterioles be given more consideration. It is also important to correlate findings in the vasculature with behavioral and neu- rological function testing.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

P.W.P. performed experiments; P.W.P. analyzed data; P.W.P. interpreted results of experiments; P.W.P. and A.M.D. prepared figures; P.W.P., C.M.D.R., N.M., and A.M.D. drafted manuscript; P.W.P., C.M.D.R., N.M., and A.M.D. approved final version of manuscript; P.W.P., C.M.D.R., N.M., and A.M.D. edited and revised manuscript; A.M.D. conception and design of research.

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