Surviving the Remodel
The Impact of Hypertension During Pregnancy

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Div erse structural and functional changes occur within blood vessels during hypertension. In relation to vascular structure, hypertension is generally associated with hypertrophy (increased cross-sectional area of the vessel wall) in aorta and other large arteries but inward remodeling (with or without increases in the cross-sectional area) in smaller resistance vessels. Inward vascular remodeling, which represents a rearrangement of the vessel wall around a smaller lumen (Figure), has been described in models of hypertension and, thus, blood flow. Thus, inward remodeling may have greater functional consequences than vascular hypertrophy.1,3

Although the term “vascular remodeling” is sometimes used rather imprecisely in studies of blood vessels, experts in the field consider inward vascular remodeling to reflect reductions in vessel diameter that are present over a range of intravascular pressures and cannot be accounted for by differences in vascular tone or vascular distensibility (vascular mechanics).2,3,5 Both hypertrophy and inward remodeling may occur in blood vessels during hypertension, but the latter change likely has the greatest impact on vascular resistance and, thus, blood flow. Thus, inward remodeling may have greater functional consequences than vascular hypertrophy.1,3

In this issue of Hypertension, Cippolla et al6 describe novel observations of changes in cerebral vascular structure brought on by hypertension during pregnancy. The findings highlight the dynamic nature of vascular remodeling under these conditions. In their study, female rats were made hypertensive using the common approach of chronic treatment with an inhibitor of NO synthase (N\textsuperscript{G}-nitro-L-arginine methyl ester). Administration of N\textsuperscript{G}-nitro-L-arginine methyl ester increased arterial pressure and produced inward remodeling of small cerebral arteries with no change in the cross-sectional area of the vessel wall (ie, eutrophic inward remodeling; Figure). When the animals then became pregnant, the reductions in vessel diameter that had occurred during hypertension were largely reversed (Figure). Because arterial pressure was not altered by pregnancy, this important determinant of vascular structure did not appear to play a role in these changes.

Previous work from this group demonstrated that pregnancy prevented changes in cerebral vascular structure in response to subsequent hypertension.7 However, these are the first findings showing that pregnancy also reverses preexisting inward vascular remodeling.

Previous studies have tested whether experimental interventions could prevent structural changes in the vasculature during hypertension. For example, treatment with a thiazide-like diuretic prevents vascular hypertrophy without preventing inward vascular remodeling in spontaneously hypertensive rats.8 These findings and others9 suggest that mechanisms that produce vascular hypertrophy differ from those that produce inward vascular remodeling. Previously, very few studies have evaluated the regression (reversibility) of inward vascular remodeling.

Many studies continue to model changes in vascular structure using aorta in vivo or aortic smooth muscle in cell culture. Although these approaches are valuable and may help to define mechanisms that contribute to vascular hypertrophy, they may not be optimal if the goal is to model the 3D rearrangement that occurs with inward remodeling in resistance vessels during hypertension. Despite the fact that inward vascular remodeling may have a greater impact on hemodynamics, few studies have examined mechanisms that produce inward remodeling during hypertension.

What mechanism(s) accounts for inward remodeling in the cerebral circulation during hypertension? Is the same mechanism involved in the regression of vascular remodeling during pregnancy? Although oxidative stress plays an important role in producing hypertrophy in cerebral arterioles, oxidative stress may not produce inward vascular remodeling.10 One mechanism that may play a key role in promoting this process involves the renin-angiotensin system. For example, hypertrophy of cerebral arterioles occurs in models of angiotensin II–dependent and angiotensin II–independent hypertension, but inward vascular remodeling occurs only with angiotensin II–dependent hypertension.9 Thus, angiotensin II may be a key determinant of inward vascular remodeling. Because vascular responses to angiotensin II are generally reduced during pregnancy,7,11 it seems possible that regression of cerebral vascular structure during pregnancy may reflect a loss or withdrawal of angiotensin II–mediated effects that promote inward vascular remodeling.

Activity of the transcription factor peroxisome proliferator-activated receptor-\(\gamma\) (PPAR-\(\gamma\)) may be another important determinant of vascular structure.12 Previous work suggested that pharmacological activators of PPAR-\(\gamma\) prevent inward remodeling of small mesenteric arteries during angiotensin II–dependent hypertension.13 Mice that express a human dominant-negative mutation in PPAR-\(\gamma\) exhibit hypertrophy...
Hypertension is a common complication of pregnancy, and pregnancy predisposes the brain to greater edema formation during acute hypertension. Cerebral vascular features of eclampsia are often similar to those seen in hypertensive encephalopathy and include breakthrough of autoregulation, marked cerebral vasodilation, and disruption of the blood-brain barrier. Seizures are a hallmark of eclampsia, and seizures produce these same physiological responses (acute hypertension and maximal cerebral vasodilation with disruption of the blood-brain barrier). Some forms of hypertension produce inward remodeling of small cerebral arteries and arterioles. By causing regression of this remodeling, pregnancy may predispose the blood-brain barrier to disruption and formation of cerebral edema during acute hypertension or seizures (Figure).

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None.

References

Figure. Schematic of structural changes in blood vessels shown in cross-section. The starting point is the vessel under control (normotensive) conditions shown on top. During chronic hypertension, vessels exhibit inward remodeling, such that the inner and outer diameter are reduced (lower right). This change increases vascular resistance, including minimal vascular resistance, and reduces transmission of pressure to the microcirculation. With hypertension during pregnancy, there is reversal (regression) of inward remodeling such that the vessel diameter returns largely to normal (bottom left). As a consequence of this outward remodeling, vascular resistance is reduced, and increases in microvascular pressure and permeability will be greater during acute hypertension or seizures. See text for additional details.

and inward remodeling in cerebral arterioles, demonstrating that PPAR-γ normally protects cerebral blood vessels against abnormal growth. Thus, changes in the activation of PPAR-γ, with the subsequent reprogramming of PPAR-γ target genes, are potential mediators of altered vascular growth during hypertension, pregnancy, and/or hypertension during pregnancy. With regard to hypertension, it is noteworthy that angiotensin II (the renin-angiotensin system) is a molecular target of PPAR-γ.

What are the functional implications of these changes in cerebral vascular structure during hypertension and hypertension during pregnancy? Inward vascular remodeling may potentially have both detrimental and protective effects in the cerebral circulation. Chronic hypertension impairs the dilator capacity of cerebral blood vessels and is a major risk factor for stroke but may also contribute to cognitive decline. Inward vascular remodeling increases vascular resistance (including minimal vascular resistance) and may particularly impact and limit cerebral blood flow under conditions that produce large reductions in cerebral vascular resistance (Figure 1). Increases in minimal vascular resistance would also limit blood flow to collateral dependent regions under low blood flow conditions or ischemia.

Inward vascular remodeling during hypertension may also protect the microcirculation from dysfunction and increases in permeability because of the transmission of elevated pressure (Figure 1). Such a mechanism may be particularly important in the brain to protect the blood-brain barrier and prevent formation of cerebral edema during acute hypertension or seizures. Although these structural changes may not influence resting cerebral blood flow, they would have a significant impact on local hemodynamics under conditions when vessels are markedly dilated (such as during break-through of autoregulation after acute hypertension).
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