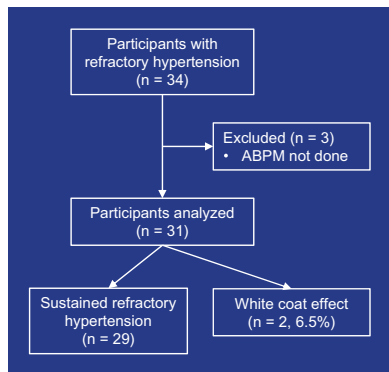
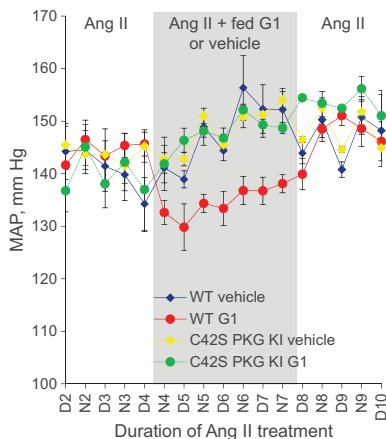


## Refractory Hypertension and White-Coat Effect (p 645)



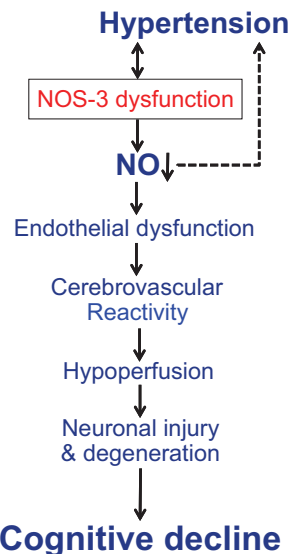
Refractory hypertension is an extreme phenotype defined as uncontrolled blood pressure (BP) despite use of  $\geq 5$  different antihypertensive agents, including chlorthalidone and spironolactone. This condition is more common among blacks and women. In the current issue, Siddiqui et al report that the white-coat effect (uncontrolled clinic BP but controlled out-of-office BP) is largely absent in patients with refractory hypertension, with a prevalence of only 6.5%. This contrasts with the 30% to 40% prevalence of a white-coat effect in less severe forms of hypertension. In the current analysis, undertreatment was excluded by requiring use of  $\geq 5$  antihypertensive medications, including chlorthalidone and spironolactone. Inaccurate BP measurement was excluded by use of an automated office BP device, according to guidelines. Medication adherence was monitored by patient self-report and medication refill rates. Patients with refractory hypertension have high ambulatory daytime and nighttime BP without a white-coat effect, a high prevalence of nocturnal hypertension (93.5%), and nondipping BP pattern (71%). Therefore, the refractory phenotype is consistent with sustained antihypertensive treatment failure, both in and out-of-office and throughout the 24-hour cycle. Such continuous lack of BP control portends increased cardiovascular, cerebrovascular, and renal risk. Preliminary studies suggest that antihypertensive treatment failure may be attributable to heightened sympathetic output. If so, sympatholytic interventions, with either medications or novel device approaches, may be of value.

## Toward a Novel Class of Antihypertensives (p 577)



PKG (protein kinase G) is a well-established end-effector kinase that mediates vasodilation and blood pressure lowering in response to agents, including NO, that increase the abundance of cGMP. The  $I\alpha$  isoform of PKG forms an intersubunit disulfide homodimer involving cysteine 42 when cellular oxidant levels are increased. This oxidative modification induces targeting of the kinase to its substrates and is associated with its activation and lowering of blood pressure. Burgoyne et al hypothesized that drugs that bind PKG  $I\alpha$  to induce or mimic the cysteine 42 disulfide will likely have therapeutic blood pressure-lowering actions. Consequently, a library of small molecules with chemical features that rendered them potentially capable of inducing PKG  $I\alpha$  oxidation were assembled, leading to identification of a compound that has been called G1. G1 lowered blood pressure in hypertensive mice in a cysteine 42-dependent manner, providing proof-of-principal for a novel class of antihypertensives that harnesses the oxidative activation of PKG  $I\alpha$ . The clinical implication is that drugs could be developed that lower blood pressure using the same mechanism of action as G1, potentially complementing existing first-line therapies. Furthermore, because existing drugs do not likely trigger PKG  $I\alpha$  oxidation, it is plausible that compounds based on G1 might be effective in patients who are resistant to current therapies. However, given the substantive armory of relatively inexpensive and effective antihypertensives and that the resistance to such therapies may be because of noncompliance, the unmet clinical need or the commercial appetite for developing such compounds may be limited.

## NO, Alzheimer Disease, and Hypertension (p 613)



Hypertension is the leading risk factor for stroke and vascular cognitive impairment and is gaining recognition as a risk factor for Alzheimer disease. Furthermore, cerebrovascular disease, leading to infarcts, white matter lesions, microbleeds, and deposition of  $\beta$ -amyloid peptide in the vessel wall (cerebral amyloid angiopathy), is common in patients with Alzheimer disease. Several clinical trials have suggested significant benefits of antihypertensive medication on cognitive performance; however, we do not know whether the normalization of blood pressure, whatever the treatment, is sufficient to prevent or slow down the progression of Alzheimer disease. In the present work, we used mouse models to differentiate between the effect of high blood pressure and of the blockade of the NO pathway on Alzheimer pathology. Our results suggest that reduced NO synthase dysfunction and NO bioavailability, necessarily linked with hypertension, result in aggravation of Alzheimer pathology and accelerate cognitive impairment, independently of the level of arterial pressure. We thus suggest that targeting hypertension, and even more importantly, preserving the capacity of the brain and cerebral blood vessels to produce physiological amounts of NO, may be promising therapeutic strategies to delay the onset and slow the progression of Alzheimer disease.

## Clinical Implications

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