

Brain Indices Predict Blood Pressure Control Aging Brains and New Predictions

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Hypertension is a predictor of dementia and is associated with subtle deficits in cognitive performance in stroke- and dementia-free individuals.¹ Younger hypertensive individuals may be as vulnerable to subtle progressive decline in cognitive ability as older individuals, although the pathophysiological mechanisms involved may be different.^{1,2} Hypertension-associated structural and functional changes in the brain begin at a surprisingly early age, and this has led to an increasing emphasis on the importance of early diagnosis and treatment.² The study by Jennings et al³ in this issue of *Hypertension* provides further support for diagnosis and treatment as early as possible in the course of hypertension. Moreover, it offers a reasonable approach to examining the efficacy of various antihypertensive classes or agents in normalizing blood pressure.

The Jennings group related indices of “brain aging” to the success of lowering blood pressure (BP) in 45 relatively healthy individuals with idiopathic hypertension and no previous history of antihypertensive medication. After structural MRI and functional position emission tomography, participants were randomly assigned in a double-blind procedure to treatment with either lisinopril (n=21), an angiotensin converting enzyme inhibitor (ACE-I), or atenolol (n=24), a β -blocking agent (β -blocker). Systolic and diastolic BPs after 1 year of treatment were related to pretreatment indices of brain aging consisting of combined ratings of ventricle and sulcal size and white matter hyperintensities and pretreatment change in regional cerebral blood flow (rCBF) in the thalamus in response to a working memory task. Together, the structural brain index and blood flow response predicted 20% of the variance in systolic BP response to treatment with adjustment for baseline BP, age, sex, and dose of medication.

There was no difference between lisinopril and atenolol with respect to the normalization of systolic BP. Nevertheless, the study contributes to the literature in several important ways: it provides evidence that the difficulty in normalizing BP with antihypertensive medications increases with brain aging, and it provides an interesting new research

paradigm for evaluating the efficacy of antihypertensive medications. Future investigations can use the research paradigm used by Jennings et al³ while exploring other predictors (indices of brain aging) in relation to treatment success.

A large clinical trial using the Jennings et al³ research paradigm will be necessary to test the hypothesis that treatment success can be achieved more readily with 1 antihypertensive agent or class of agents than another. Although Jennings et al³ did not find differences between the drugs in terms of normalizing systolic BP after 1 year, it is possible that, because the study may have had insufficient power to detect a difference, the 2 drugs compared do differ. Clearly there is evidence supporting the choice of these drug types in terms of vascular remodeling and cerebral blood flow.⁴ As pointed out by Jennings et al,⁵ neither passes the blood-brain barrier, thus allowing the results to be interpreted in terms of vascular, rather than neuronal, effects; and in some studies, in comparison to β -blockers, ACE-Is reverse the peripheral vascular remodeling that occurs with hypertension. Thus, ACE-Is and β -blocking agents, as well as other antihypertensive medications, eg, angiotensin-receptor blockers, remain good candidates for larger trials. A recent study suggests that aliskiren and cotreatment with valsartan, an angiotensin II receptor blocker, may be good candidates for inclusion in future trials. Aliskiren, a renin inhibitor, was associated with NO bioavailability and was protective with respect to endothelial function and atherosclerotic changes in a rabbit model.⁶ The combination of aliskiren and valsartan had additive protective effects on endothelial function and atherosclerotic changes. Obviously, there are other antihypertensive drugs that are good candidates for trials where the ultimate goal is to reduce BP to lower the incidence of dementia.²

In terms of cost-effectiveness, it may be important to address some key questions raised by the Jennings et al³ study before a larger clinical trial. For example, is provocation of an active rCBF response by a working memory task an essential element of the protocol? It may be a key element, because information-processing tasks elicit active changes in the regional distribution of blood flow, thus providing metabolic support to neural areas.⁵

Do other information processing tasks, eg, episodic memory or executive functioning, afford a better or poorer prediction of treatment success, and, if so, are results specific to the thalamic region? Working memory-provoked rCBF activity in the parietal region added nothing to the prediction. The brain regions chosen for the Jennings et al³ study were based on previous work in their laboratory. Larger studies with more statistical power might profitably examine the parietal area and others brain regions shown to be associated with elicited and “resting” rCBF.⁷

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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Two additional questions arise from the first: is stimulation of rCBF activity by a cognitive task necessary, or are other established provocateurs of rCBF activity equally or more effective in achieving the level of prediction of BP control obtained; and does information processing–elicited rCBF afford the same or better prediction of treatment success than resting rCBF? A recent study using resting rCBF indicates that hypertension is associated with greater 6-year longitudinal decline in resting rCBF in middle and inferior prefrontal regions, the anterior cingulate gyrus, occipitotemporal regions, and in visual association cortices.⁷

Given recent arguments for the importance of achieving control over central BP, as opposed to peripheral BP, it would seem important to compare ACE-Is and β -blockers using measures of central BP values as the outcome measures. Recent work suggests that reduction in central BP may be a better outcome variable when comparing ACE-Is and β -blockers. Over 1 year of treatment, subjects treated with ACE-Is showed a greater decrease in peripheral systolic BP than those treated with β -blockers, and this difference in BP lowering was more pronounced for aortic and carotid systolic BP.⁸ Also, there is some evidence that β -blocking agents may be ineffective in lowering central BP.⁹

The exciting feature of work in Jennings' laboratory is that it considers the "flip side" of the relations between cognition and rCBF.⁵ Cerebral blood flow dynamics not only influence cognition, but the reverse is true.^{3,5} This opens exciting new areas of research for those of us who study hypertension and cognition. The Jennings et al³ paradigm will contribute important information to population-based studies of effective treatment strategies at different ages. Will research based on these investigations eventually lead to an individualized patient treatment approach based on the recognition that there are individual differences in brain function and structure that affect BP over time? In 1988, Streeten and Anderson¹⁰ summarized 15 years of endocrine-based studies of what they termed "a rational therapeutic approach" to patients with hypertension. They note that, "it is evident from the results obtained in these studies that improved control of hypertension was accomplished in almost 50% of patients by determining and treating the responsible pathogenetic mechanisms" [pg 190]. Streeten and Anderson¹⁰ were investigating the best treatment approaches to normalizing BP based on mechanism. Many others continue in this tradition. It seems to us that the presumably less-costly stepped-care approach

and its recent variants have prevailed over these presumably more rational methods. Jennings et al³ are examining the best treatment strategies to use based on hypertension and age-related changes in brain pathophysiology. It is our hope that, with reduced cost and improved safety and convenience of structural and functional imaging studies, this early progress will lead to individualized approaches to patient treatment.

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