Endothelin (ET) receptor antagonists are an established treatment for pulmonary arterial hypertension and scleroderma digital ulceration, and they show promise in chronic kidney disease and resistant hypertension. Their use may be limited by salt and water retention. Animal studies suggest that this might be because of unwanted renal tubular ETB receptor blockade. Previous attempts to determine whether this mechanism operates in man have been confounded by the hemodynamic consequences of endothelin receptor stimulation. In this issue, Hunter et al report the results of a randomized, placebo-controlled crossover study in healthy volunteers receiving subpressor doses of the endothelin-1 precursor, big endothelin-1. Because there were no significant changes in systemic hemodynamics or glomerular filtration rate, they were able to study the direct effects of endothelin-1 signaling on renal tubular salt and water transport. Big endothelin-1 increased the fractional excretion of sodium, free water clearance, and the urinary abundance of the sodium–potassium–chloride cotransporter, NKCC2. Their results suggest that, in the human kidney, endothelin-1 stimulates sodium reabsorption in the thick ascending limb and suppresses sodium reabsorption in the distal tubule. The authors suggest that the fluid retention associated with endothelin receptor antagonist therapy might be improved by the co-prescription of potassium-sparing diuretics and propose a clinical trial to test this hypothesis. These novel mechanistic insights could allow the therapeutic potential of these agents to be realized.

Calcineurin inhibitors (CNIs) are widely used for maintenance of immunosuppression in patients with solid organ transplants and autoimmune disorders. However, a limiting factor in the use of the CNIs cyclosporine A and tacrolimus is the development of cardiovascular and renal toxicity, leading to organ dysfunction and hypertension. It is therefore important to understand and prevent the toxic cardiovascular and renal effects of chronic CNI therapy. Previous reports have shown that CNIs reduce anti-inflammatory regulatory T cells while increasing proinflammatory IL-17 (interleukin-17)–producing T helper cells, despite reducing the overall number of T cells. We hypothesized that all-trans retinoic acid, reported to both increase regulatory T cells and decrease IL-17–producing T helper cells, would augment Tregs and prevent the development of vascular and renal injury and hypertension induced by CNIs. Treatment with either retinoic acid or an IL-17-neutralizing antibody increased Treg levels and prevented the hypertension, endothelial dysfunction, and vascular and glomerular injury caused by CNIs. We suggest that retinoic acid and IL-17-neutralizing antibodies, currently approved by the Food and Drug Administration, be considered as adjuvant therapy in patients receiving CNIs.

Orthostatic hypotension (OH) is a simple marker of blood pressure variability. Several studies indicate a potential link between OH and incident dementia, but without substantial evidence to date. Seven thousand four hundred and twenty-five subjects from the Three-City study with lying and standing blood pressure at baseline were followed ≤12 years and screened every 2 years for dementia. After multivariable adjustment, Cox regression analysis and illness-death model analysis showed that whatever the threshold chosen for the diagnosis of OH, OH is associated with an increased risk of dementia of ≥25%. This association highlights the relationship between blood pressure and dementia. In midlife adults, we have evidence that high blood pressure is associated with an increased risk of dementia. For elderly individuals, we now have evidence that blood pressure variability in its own right (and not the blood pressure level per se) is associated with increased risk of dementia. Blood pressure surges accompanied by an impaired cerebral microcirculation are most likely responsible for repeated episodes of ischemia. In the elderly, OH seems to be more likely a marker of vascular aging than a marker of dysautonomia because OH is better linked to vascular dementia than to Alzheimer disease. Finally, the study may raise the question of the need to take into account measures of blood pressure variability (particularly OH) in individuals at increased risk of dementia and to test whether tackling OH could reduce the incidence of dementia.

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**Calcineurin Inhibitors, Immune Cells, and Hypertension (p 183)**

**Orthostatic Hypotension Is Associated With Incident Dementia (p 44)**
Clinical Implications

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