Hypertension is the major risk factor for heart failure with preserved ejection fraction (EF), and abnormalities of diastolic function are prevalent in patients with hypertension who have not progressed to clinical heart failure with preserved EF. Systolic function as assessed by EF is normal in the majority of these patients, but a link between systolic and diastolic function has long been suspected. The phenomenon of shortening deactivation whereby shortening of cardiomyocytes leads to a rapid decrease in tension provides a potential link between systolic and diastolic function. We formulated a novel measure of early systolic ejection, first-phase EF, likely to provide a measure of ventricle fiber shortening that triggers relaxation. We found a graded relationship between first-phase EF and diastolic function as measured by E/E′ (the ratio between early mitral inflow velocity and mitral annular early diastolic velocity) independent of measures of afterload or other confounding factors (Figure). These results provide a novel paradigm to understand a functional link between systolic and diastolic function and suggest that first-phase EF may be an important diagnostic marker and therapeutic target for preventing or treating heart failure with preserved EF.

Even though a commonly accepted core mechanism in fluid volume and blood pressure regulation is that there is a parallel relationship between body Na⁺ and extracellular fluid content, long-term observations in humans have shown that considerable amounts of Na⁺ are retained or removed from the subjects’ bodies without commensurate water retention or loss. Na⁺ could thus be stored somewhere in the body without commensurate water retention and thereby be inactive from a fluid balance viewpoint. This implies that there is not a strict isotonicity of all body fluids. Skin electrolyte concentrations may not necessarily equilibrate with blood electrolytes, and any electrolyte accumulation in excess of water might cause local hypertonicity. We have investigated whether salt accumulation in skin induced by high-salt diet or deoxycorticosterone acetate (DOCA)-salt treatment results in interstitial fluid that is hypertonic relative to plasma. Wick fluid returned to the general circulation, were isosmotic to plasma. Elution experiments showed that there is an osmotic gradient from superficial to deeper layers of skin (Figure), suggesting that the skin may differentially control its own microenvironment and together with the kidney actively participate in fluid volume regulation. A more detailed assessment of these electrolyte gradients in higher resolution may lead to a better understanding of how to remove tissue salt that accumulates in skin and muscle in various pathological conditions.

**CLINICAL IMPLICATIONS**

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**Hypertension** is available at http://hyper.ahajournals.org

DOI: 10.1161/HYPERTENSIONAHA.117.09149
Clinical Implications

Hypertension. 2017;69:521
doi: 10.1161/HYPERTENSIONAHA.117.09149

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