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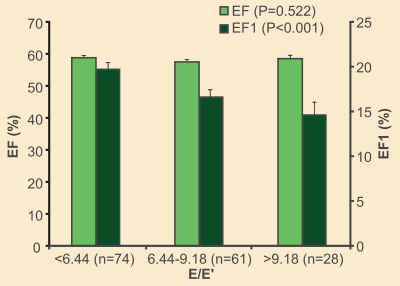
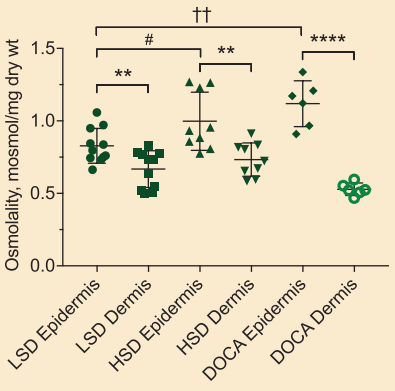
Shortening Deactivation and Diastolic Function (page 633)



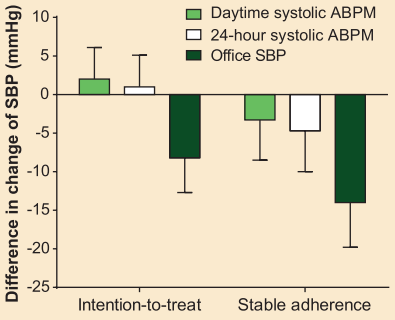
Hypertension is the major risk factor for heart failure with preserved ejection fraction (EF), and abnormalities of diastolic function are prevalent in patients with hypertension who have not progressed to clinical heart failure with preserved EF. Systolic function as assessed by EF is normal in the 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.

Interstitial Fluid and Lymph in Hyperosmolal Skin (page 660)

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 and lymph, which may both represent interstitial fluid during steady state conditions and be representative of interstitial fluid returning 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.



Medication Adherence and Effect of Renal Denervation (page 678)



SYMPATHY, an open-label randomized controlled trial in apparent resistant hypertensive patients, had as a primary end point change in daytime systolic ambulatory blood pressure (BP) 6 months after renal denervation (RDN) compared with usual care. This trial adds important information to what usual care actually is because BP-lowering drugs were assessed in blood sampled at baseline and after 6 months. Patients and physicians were unaware of the adherence assessments. Our intention-to-treat analysis (N=139, 95 RDN) showed no additional reduction in daytime systolic ambulatory BP with RDN compared with that in usual care (+2.0 mm Hg [−6.1 to 10.2]). In only 1 out of 5 patients of the subgroup (n=98) in whom drug levels were assessed, were all prescribed medications detected. Moreover, in 31% of patients, the level of adherence changed during the trial. Analysis of the patients with stable level of adherence revealed that daytime systolic ambulatory BP declined 3.3 mm Hg (−13.7 to 7.2) more in favor of RDN (Figure). The same trend was observed for 24-hour systolic ambulatory BP and office SBP. The results of the SYMPATHY trial suggest that (1) RDN is not superior to usual care in lowering BP, (2) poor adherence could partially explain the condition of resistant hypertension, and (3) objective assessment of medication adherence is mandatory in intervention trials because changes in adherence greatly affect the ability to assess the effect of an additional treatment.

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