Published in final edited form as:

J Am Coll Cardiol. 2020 December 15; 76(24): 2830–2833. doi:10.1016/j.jacc.2020.10.028.

Unpreserved lymphatic reserve in heart failure with preserved ejection fraction

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Keywords

heart failure; lymphatics; microvascular function

Understanding of heart failure with preserved ejection fraction (HFpEF) continues to evolve, shifting from a cardio-centric to more encompassing paradigm inclusive of vascular and systemic pathophysiology. Among the underlying mechanisms expounded for HFpEF, one model posits structural and functional alterations in the arterial vasculature, particularly coronary microvascular rarefaction and mismatch between blood flow and oxygen demand (1,2). Coronary microvascular dysfunction strongly associates with peripheral arterial microvascular dysfunction, collectively suggesting a systemic vascular phenotype in patients with HFpEF (3).

Paralleling this broadened scope beyond the heart, investigation of the vasculature in HFpEF is also expanding from an arterial-centric view to examine other vascular beds, including veins and, more recently, lymphatics. Mechanistic studies in rodents demonstrate the significance of lymphatics in regulating interstitial sodium via immune cell-mediated lymphangiogenesis (4). When lymphatic clearance is impaired in the skin, excess tissue sodium collection, interstitial volume expansion, and poor blood pressure control ensue (5). In human disease, skin sodium storage is observed using sodium magnetic resonance imaging (^{23}Na-MRI) in patients with hypertension (6), diabetes (7), and chronic kidney disease (8). Although these are key comorbidities of HFpEF, data linking peripheral lymphatic microvascular dysfunction and interstitial volume or sodium dysregulation in HFpEF are sparse.

In this issue of the *Journal*, Rossitto and colleagues help fill this gap with results from the HAPPIFY (Heart fAilure with Preserved ejection fraction: Plethysmography for Interstitial Function and skin biopsY) study (9). Through an extensive *in vivo* and *ex vivo* analysis, the authors present a compelling link between peripheral lymphatic and arterial microvascular

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dysfunction and interstitial fluid retention in patients with HFpEF. HAPPIFY included stable ambulatory subjects with HFpEF (n=16) and a healthy control group (n=16) of similar age and sex distribution. Study procedures included gluteal tissue biopsy for measurement of skin water, sodium, and potassium content, histochemical staining of the microvasculature, and quantification of gene expression of lymphatic markers. Venous occlusion strain gauge plethysmography of both the calf and forearm under increasing hydraulic pressures allowed calculation of two key measures of fluid homeostasis: 1) isovolumetric pressure, defined as the pressure above which edema develops when extravasation exceeds lymphatic drainage, and 2) peripheral microvascular filtration coefficient, defined as the rate of tissue fluid accumulation.

The HFpEF group had a higher mean body-mass index (BMI) than controls (median ~34 vs. 25 kg/m^2) and a typical HFpEF comorbidity profile; namely, high prevalence of hypertension (94%), atrial fibrillation (69%), diabetes (44%), and chronic kidney disease (44%). Peripheral arterial pressures were similar, and venous filling pressure in the calf was modestly higher among subjects with HFpEF compared with controls (median 7 [7-9] vs. 5 [4-5] mmHg; $p<0.001$), though not suggestive of marked venous congestion. Isovolumetric pressure was lower in patients with HFpEF compared with controls (forearm: 17 ± 4 vs. 25 ± 5 mmHg; $p<0.001$; calf: 16 ± 4 vs. 22 ± 4 mmHg; $p=0.003$). In other words, in the extremities of patients with HFpEF, extravasation exceeds interstitial fluid drainage at a lower pressure than in control subjects, suggesting reduced lymphatic reserve capacity.

Contrary to the investigators' original hypothesis, however, the peripheral microvascular filtration coefficient was lower in the calves of subjects with HFpEF compared with controls (median 3.30 [2.33-3.88] vs. 4.66 [3.70-6.15] $\mu l \times 100ml$ of $tissue^{-1} \times min^{-1} \times mmHg^{-1}$; $p=0.008$). In line with this, subjects with HFpEF displayed rarefaction of both arterial and lymphatic dermal microvessels, suggesting reduced vascular surface area could limit fluid exchange rate at the capillary level. Expression of lymphatic markers Prox-1 and Lyve-1 was also decreased in HFpEF. Tissue chemical analysis revealed dry-weight sodium was lower in the deep dermis of patients with HFpEF, likely related to increased fat content in this group with obesity. No difference in sodium was found, however, when adjusting for parallel water content. This finding is consistent with other work by the authors suggesting sub-dermal lymphatics may respond to biomechanical pressure of interstitial Na^+ with water retention (i.e. edema) (10).

The collective data indicate an abnormal molecular, structural, and physiological peripheral lymphatic phenotype in at least a subset of patients with HFpEF. Despite these provocative data, a few limitations are notable. The cross-sectional design precludes inferences regarding causality. Venous pressure was quantified in limbs, not centrally, and was not included in adjusted analysis. The impact of medications, in particular how acute withholding of diuretics on the study day could have influenced lymphatic reserve, is uncertain. The substantial differences in comorbidity profile between HFpEF and control subjects are notable as, for example, obesity itself contributes to an inflammatory tissue profile linked to lymphatic dysfunction (11). B-type natriuretic peptide (BNP) increases lymphatic permeability (12), raising the question of whether the findings reflect, in part, a response to higher BNP rather than specificity for HFpEF.

Nonetheless, the authors should be lauded for their extensive and novel characterization of peripheral lymphatic function providing added depth to our understanding of HFpEF. Valuable scientific contributions also reveal new questions and opportunities; the work by Rossitto and colleagues certainly does so. For example, how should we utilize these intriguing findings clinically? Performing skin biopsies with chemical analysis and plethysmography is not feasible for implementation in clinical practice. Alternatively, non-invasive imaging strategies sensitive to tissue sodium (13) and lymphatic physiology (14) are emerging to visualize lymphatic disease mechanisms (Figure). Applying these imaging techniques in a broader range of patient phenotypes and in response to interventions may help answer questions ensuing from this work. For example, is lymphatic related pathology a defining and universal feature of HFpEF, the broader HF population, or part of a complex interplay involving obesity, inflammation, venous insufficiency, and overt limb lymphedema in a subset of individuals? What are the impacts of pharmacotherapies (e.g. diuretics, SGLT-2 inhibitors, neprilysin inhibition, LTB4 inhibitors, etc.) on lymphatic clearance function in patients with and without HF? Does lymphatic associated pathology precede HF onset or occur as a consequence?

Overall, the new evidence for unpreserved lymphatic reserve adds to the expanding recognition of impaired reserve of many systems, including cardiac, arterial, skeletal muscle, and others in patients with HFpEF (15). This deeper understanding of HFpEF provides direction towards development and testing of treatment strategies to target preservation and restoration of “reserve” to decrease the burden of HFpEF.

Sources of Funding

Gupta: K23HL128928, R01HL133860, R01HL148661; Crescenzi: AHA18CDA34110297, AHA19IPLOI34760518, Lipedema Foundation Collaborative Award #12; Aday: NIH K12 HL133117

Disclosures

Gupta: research support from Imara, Inc.; Crescenzi: none; Aday: consulting for OptumCare.

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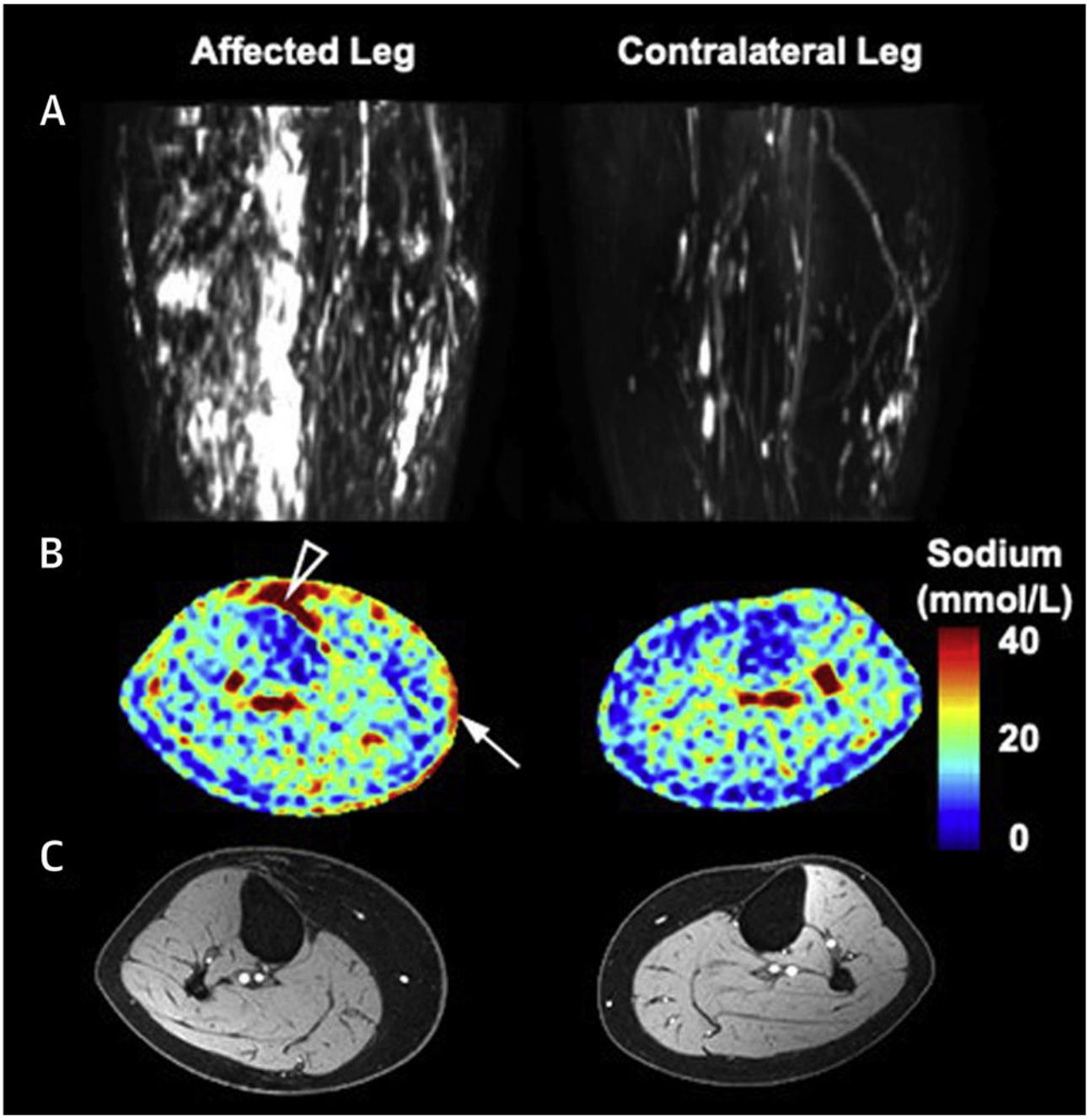

Figure. Non-invasive imaging of lymphatic and sodium physiology to understand edema.

Example MR lymphangiography and sodium MRI in a patient with overt lymphatic disease due to unilateral leg lymphedema. A) Long turbo-spin-echo 3.0T MR lymphangiography (displayed as the maximum intensity projection) shows contrast asymmetry between affected and contralateral limbs. B) ^{23}Na-MRI reveals tissue sodium deposition in the affected compared with contralateral limb, particularly in the skin (arrow) and subcutaneous adipose tissue (arrowhead), consistent with lymphatic mechanical insufficiency. C)

Conventional water-weighted MRI allows coregistration for identifying regions of interest on the ^{23}Na-MRI scan.