LUMEN EXPANSION AT FIVE LOCATIONS ALONG THE VENOUS SYSTEM OF MURINE MODELS

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PURPOSE: To quantify lumen expansion along the venous system in murine models with and without a vascular challenge. The target audience is MRI labs focused on cardiovascular disease of the venous system, biomechanics, combining MRI with computational fluid dynamics, and translation.

INTRODUCTION: Cardiovascular (CV) disease is the number one killer among non-communicable diseases in the United States[1] and worldwide[2], costing the US over $300 billion annually.[3] Deep vein thrombosis (DVT) affects an estimated 900,000 people in the US each year.[4] However, the venous system is understudied, a discrepancy which must be urgently corrected as the US population with DVT is projected to double by 2050.[5]

Biomechanical forces are foundational in the CV system, promoting healthy adaptation or maladaptation in the case of disease. Basic parameters such as flow and pressure are known to differ in the venous system compared to the arterial system. Forces such as wall shear stress and wall motion, however, have yet to be well-defined in the venous system. This work focuses on the latter, comparing wall dynamics along the venous system of murine models in physiological conditions. This is critical since knowing normal physiological parameters lays the foundation for studying pathological conditions.

METHODS: Experiments were performed with IACUC approval. 14-16 week old C57BL6 mice (5 male, 5 female) were anesthetized using isoflurane and imaged at 7T using a 40mm diameter volume coil (Agilent Technologies, CA). 2D and 3D gradient echo data (Fig 1) were used to plan ECG-gated acqu isitions that included 12 CINE frames across the cardiac cycle (Fig 2). CINE data were acquired at five locations (femoral and iliac veins, infra- and supra-renal vena cava (VC), jugular vein; TR/TE: ~110ms (period of cardiac cycle)/2-5ms depending on bandwidth, FOV: (30mm)^2, matrix: 256^2 zero-filled to 512^2 for an in-plane resolution of 59 μm^2, slice thickness: 1 mm except suprarenal = 0.7 mm due to nearby branching vessels, NEX: 8). Temperature, respiration and cardiac rate were monitored and/or controlled, the last of which was used to prospectively trigger off of the R-wave (National Instruments, TX; SA Instruments, NY). At locations where vein and artery abut one another, arterial flow was saturated in order to facilitate semi-automatic segmentation of the vein. Vessel area was quantified in each CINE frame and normalized to the smallest area, assumed to be diastole (MRVision , MA). Typically, mean + 5 standard deviations of nearby stationary tissue signal intensity was used to set a threshold value for segmentation.

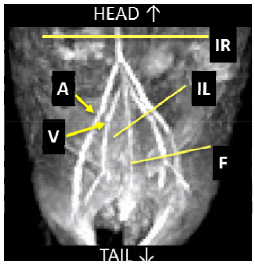

Fig 1: 3D maximum intensity projection used to plan CINE acquisitions at the infrarenal (IR), iliac (IL), and femoral (F) locations. Iliac arteries (A) and veins (V) are visible.

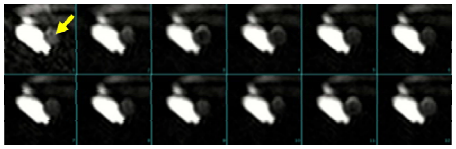

Fig 2: Axial slice of infrarenal vena cava. The aorta (arrow) has been nulled with a preparatory pulse proximal to the slice. Note that the aorta appears to impinge on the vena cava in this location. The vena cava in this region is ~75-135% larger than the aorta, depending on the point in the cardiac cycle.

RESULTS: Body weights of male and female mice were 27.2 +/- 1.1 g and 21.7 +/- 1.2 g. Temperature, respiration and heart rate during image acquisition were: 37.1 +/- 0.2 °C, 71 +/- 8 breaths/min, and 553 +/- 62 beats/min. Imaging parameters resulted in ~10 (femoral) to 30 (suprarenal) pixels across veins. The venous system departs from the nearly circular shape seen in the arterial system (Fig 2). This was most prominent in the infra- and supra-renal VC. Non steady-state effects seen in initial CINE frames will be compensated for in future acquisitions (data not shown). The minimum and maximum vessel area along the venous tree during the cardiac cycle is illustrated in Figure 3. Starting at the femoral vein and comparing the proximally adjacent location only, area increased ~1.9-,1.4-, and 2.5-fold. Veins ranged from 75 - 250% larger than corresponding arteries in the abdominal cavity and lower limbs. The jugular vein was ~500% larger than the carotid artery and ~4-26% larger than even the infrarenal VC. Gender did not appear to influence lumen expansion at any location (Fig4) and maximum lumen expansion ranged from ~4 to 13% greater than diastole, less than half the expansion typically seen in the arterial system.[6]

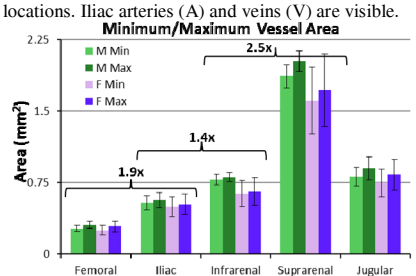

Fig 3. Minimum/maximum vessel area (mean, std error) at five locations along the venous tree in murine models.

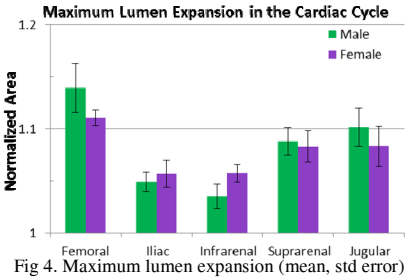

Fig 4. Maximum lumen expansion (mean, std error) at five locations along the venous system in murine models.

DISCUSSION: The venous system has reduced flow velocities and pressure compared to the arterial system. In addition, it has supplementary structures such as valves to move blood back to the heart, particularly relevant for flow from the lower limbs which must work against gravity, although this is less significant in quadrupeds. Combined, these factors all likely contribute to reduced lumen expansion throughout the cardiac cycle. Although this may not be surprising, the results of this study are critical and necessary to establish baseline characteristics of the rodent preclinical models we use as surrogates for the human condition.

Summarizing the importance of this work: 1) Physiological conditions were fastidiously monitored and controlled, particularly important when making measurements in the CV system; 2) This is some of the first biomechanics data acquired *in vivo* in the venous system of small preclinical models; 3) Wall dynamics are known to influence wall thickness and material content and, therefore, are likely pertinent with respect to mechanisms which promote DVT; 3) It expands upon and complements previous studies performed solely in the abdominal aorta of mice;[4] 4) It provides baseline measurements that will be compared to: other species, changes upon inducing a vascular challenge, and changes due to the development of DVT; and, 5) It already incorporates data to address the recent emphasis on sex-balancing in biomedical research.[7]

Immediate future work will be focused on improved data analysis and acquiring data with a pharmacologically induced vascular challenge (dobutamine). Regarding the former, rodent preclinical investigations allow for larger numbers of animals, resulting in a large amount of data to be analyzed. Our efforts will be focused on developing semi-automated analysis that will improve segmentation reproducibility by reducing user bias and allow for quantification of metrics such as perimeter/cyclic strain, centroid motion, and (a)symmetry by looking at major and minor axes of the vessel through the cardiac cycle. In smaller vessels, inaccurately assessing whether even a single voxel is included as part of the flow lumen can result in ≥ 10% error; analysis improvements will be critical for correct assessment. The quality of the comprehensive data presented here will allow development and implementation of such analysis methods.

(Please note: These data are complementary to and independent from work in the arterial system submitted in a separate abstract. They share similar methodology but the data and conclusions are not duplicative in any way.)**1.** World Health Organization - *NCD Country Profiles*, 2011. **2.** World Health Organization - *Global status report on non-communicable diseases,* 2010. **3.** Ruckley, et al. *Angiology.* 1997;48:67-9. **4.** Heit, et al. *Blood.* 2005;106:267A. **5.** Deitelzweig, et al. *Am J Hematol.* 2011;86:217-20. **6.** Goergen, et al. *JMRI.* 2010;32:847-58. **7.** Clayton and Collins. *Nature.* 2014;509:282-3.