Implementation, validation, and application of cine PCMRI for quantifying blood flow in small animal models of cardiovascular disease

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Introduction

The ability to easily manipulate the murine genome in order to examine the contribution of specific genes or molecules to normal and pathological states has made it increasingly important to understand how physiology, pathogenesis, and therapeutic development scale from mouse to human. Most investigations to understand how parameters scale from mouse to human have focused on metabolic measurements such as pharmaco -kinetics and -dynamics. Less is known about how *in vivo* hemodynamic conditions (e.g. shear stress), particularly important in the localization and progression of vascular disease, scale from mouse to human.

Work investigating hemodynamics in small animal models has primarily been derived from invasive or acute studies acquiring mean flow rates using Doppler transonic flow probes. Phase contrast MRI (PCMRI) has rarely been applied to small animal models due to challenges associated with temporal and spatial resolution (*ex vivo* [1]; *in vivo* to study myocardial motion [2]). PCMRI in small animal models could be coupled with anatomical MRI data and computational fluid dynamics (CFD) simulations, analogous to what has been successfully accomplished for human and large animal studies [3], to obtain data on how regional hemodynamic parameters vary from mouse to human in normal and pathogenic states. The non-invasive nature of the technique would allow for longitudinal investigation in the same animal, enabling the ability to quantify changes in hemodynamic parameters during disease progression, e.g. abdominal aortic aneurysms, which is infeasible in human patients due to the long time scale of the pathogenesis.

The work presented here describes implementation, *in vitro* validation, and *in vivo* application of a through-plane PCMRI sequence on a 4.7T small-bore scanner. Non-invasive measurements of *in vivo* blood flow velocities through the infrarenal abdominal aorta of both rats (n=5) and mice (n=5) were reproducibly acquired.

Materials and Methods

All experiments were performed with local IACUC approval in accordance with ethical guidelines. Male 8-12 week old Sprague Dawley rats and male 8-12 week old C57BL6 mice were used.

MRI was performed at 4.7T using an Inova console (Varian, Inc., Palo Alto, CA). The through-plane PCMRI sequence involved repeated measurements using reversed, bipolar, linear gradients (TR/TE 13/3.2ms, FOV (6cm)^2 or (3cm)^2, matrix 128^2 zero-filled to 256^2, slice thickness 2mm, NEX = 8, 12 frames, venc = 200cm/sec). *In vitro* validation utilized tubing with a diameter approximating a rat's aorta (3mm), included a range of steady flow velocities, and a pulsatile phantom with a period comparable to a rat's heart rate (5Hz) and velocities predicted to be seen *in vivo*. The effect of non-steady state acquisition due to prospective gating was evaluated and the proper order of baseline corrections (0th, 1st, or 2nd) needed to compensate for remaining phase errors after subtraction of the two acquisitions was analyzed. For *in vivo* data collection, a 6cm or 3cm inner diameter volume coil was used to image rats or mice, respectively. Animals were anesthetized using isoflurane and body temperature was maintained between 36-37C throughout imaging. Two subcutaneous ECG leads and a respiratory monitor (SA Instruments, Inc., NY) were utilized for prospective triggering off of the R-wave during exhalation only. The boundary of the aorta was defined using magnitude and velocity images using MRvision software (Winchester, MA).

Results

In vitro: Measurements at a range of velocities demonstrated no effect due to prospective gating (Figure 1a). Volumetric flow calculated from PCMRI data from a pulsatile phantom agreed well with flow probe measurements (Figure 1b).

In vivo: A series of scans in the same animal to assess repeatability demonstrated the need to exchange phase encode and readout direction during data acquisition to minimize the effect of chemical shift artifact on properly defining the boundary of the aorta. *In vitro* and *in vivo* data were used to determine that a linear baseline correction best rectified remaining static phase errors in both rat and mouse data; resulting velocities in static tissue were less than ±2cm/sec. This analysis was of particular importance due to the inability to use static regions from the area ventral to the aorta because of ubiquitous phase artifacts associated with the digestive tract. A representative velocity image and corresponding plots of blood flow velocities in the infrarenal abdominal aorta, at 12 timepoints through the cardiac cycle, for all rats and mice are shown in Figure 2. Data acquisition took approximately 16 minutes per animal.

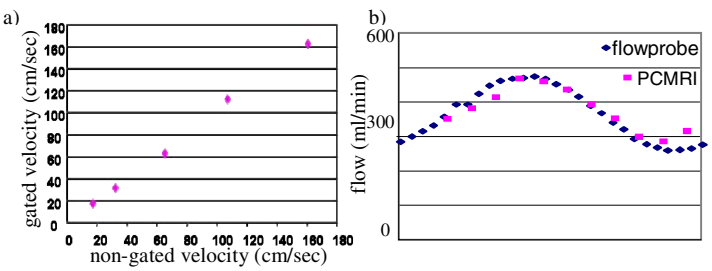

Figure 1. a) *In vitro* assessment of prospective gating showed no effect on PCMRI measurements (R^2=0.99). b) Values of pulsatile flow were measured accurately with PCMRI.

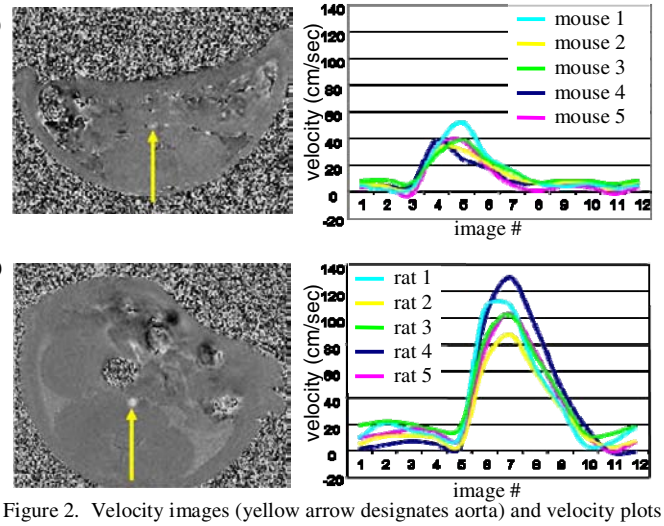

Figure 2. Velocity images (yellow arrow designates aorta) and velocity plots from mouse (a) and rat (b) cohorts. PCMRI measurements were reproducible.

Discussion

This work shows that with careful implementation and validation, application of PCMRI to small animal models can be reproducibly accomplished with reasonable scan times (16min/animal). Of interest is the fact that velocities measured in mice and rats were either similar to or larger than, respectively, values seen in the human aorta [4], a fact perhaps not yet recognized [5]. Approximations of Reynold's number in normal aortas, therefore, are largely determined by geometry (mouse: 80, rat: 480, human: 1600). Initial CFD simulations performed on solid models reconstructed from anatomical MRI data derived from the same five mice and rats, and using the animal specific PCMRI flow waveform as theinlet boundary condition, resulted in mean wall shear stress values of 76 and 60 dynes/cm^2, respectively, compared to human values of 5 dynes/cm^2. These results agree with the allometric scaling law relating shear stress (τ) to body mass (M) ($\tau \propto M^{-0.2}$) [6] but suggest an exponent of -0.37 (R^2 = 0.94) instead. Allometric laws that describe the relationship between an organism's body parts or processes provide a way to predict physiology in one organism based on data from another, possibly of very different size. The data derived from the application of PCMRI to small animal models of cardiovascular disease may provide translational insight necessary to more rapidly develop novel therapeutic approaches to treat diseases of the cardiovascular system.

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