Allometric scaling of wall shear stress from mice to humans: quantification using cine phase-contrast MRI and computational fluid dynamics

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Submitted 16 March 2006; accepted in final form 7 May 2006

Allometric scaling laws that describe the relationship between structural or functional characteristics and body mass provide a way to relate physiology in organisms of very different size. Such allometric laws take the form of \( Y = Y_0M^b \), where \( Y \) is the structural or functional parameter of interest, \( Y_0 \) is a normalization constant for the quantity of interest, \( M \) is body mass, and \( b \) is the scaling exponent. Most allometric investigations have focused on geometry or metabolic processes. Less is known about how biomechanical forces, particularly influential in the cardiovascular system, scale across species.

The importance of the cardiovascular system is underscored by the fact that most cells throughout the body are within 50 \( \mu \)m of a capillary bed (50), which allows diffusion of requisite nutrients to tissue after convective transport through the macrocirculation. Of the biomechanical forces experienced in the cardiovascular system, wall shear stress (WSS, \( \tau \)) is a primary determinant of the health or disease localization/progression (12, 33, 43, 53) in this organ system, macroscopically and microscopically. WSS contributes to the regulation of vessel geometry [acutely (34) and chronically (24)], the morphology and orientation of endothelial cells (30), and cellular differentiation (38). In addition, a shear stress response element has been identified in the promoter region of several genes whose expression is known to be modified with changes in shear stress (37). Despite the importance of WSS in vascular biology, only Langille (23) has explicitly proposed an allometric relationship for WSS in the aorta, estimating a scaling exponent of \( b = -0.2 \), using historical data collected for cardiac output and an allometric relationship for radius that has since been revised.

Quantification of WSS requires the measurement of vessel geometry and blood flow, ideally in vivo by noninvasive methods. Accomplishing this in small animal models is difficult because of challenges associated with achieving adequate spatial and temporal resolution due to diminutive geometry and rapid heart rates, respectively. Typical methods to measure vessel geometry (caliper or photographic) require actual visualization of the vessel of interest by surgical exposure; although this can be serially repeated, it neglects geometric information in the anterior-posterior direction and is usually limited to measurements at discrete locations. An alternative, vascular casting, is terminal and relies on closely controlling methodological parameters, e.g., pressure, during the procedure. Casting techniques can provide three-dimensional (3D) imaging.

LONGITUDINAL INVESTIGATION of cardiovascular diseases is typically not feasible in human patients because of the long time scale of pathogenesis. Small animal models of cardiovascular disease represent an appropriate alternative because of the ability to create (by dietary, surgical, or genetic manipulation) disease states closely mimicking those seen in humans [atherosclerosis (11, 35), aortic aneurysm (4, 7), myocardial infarction (5, 48), congestive heart failure (44), and peripheral arterial disease (41)]. In particular, the ability to easily manipulate the murine genome 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 approaches scale from mouse to human.
data along a large extent of vasculature but have been shown to consistently underestimate vessel diameter if pressure fixation precedes casting and overestimate bifurcation angles if performed in situ (29). The most common methods to quantify blood flow in small animal models (e.g., Pick, dilution, radioactive microspheres, or Doppler flow probe) are confounded by similar limitations. They are invasive, hindered because of small blood volumes (36), and can have high variability, even in larger species (32). Furthermore, these methods are typically used to acquire mean flow rates rather than temporally resolved flow data through the cardiac cycle, cannot provide spatially resolved velocity data across the vessel lumen, and are incapable of making serial measurements without appreciably perturbing the vessel of interest. High-frequency ultrasound imaging systems appropriate for small animal applications can provide a noninvasive alternative for measuring geometry (13) and blood flow (25) in vivo. However, this modality can be user-dependent and difficult to apply over a large extent of anatomy, especially if complicated out-of-plane geometry is present, e.g., bifurcations.

Magnetic resonance imaging (MRI) is capable of overcoming these limitations in quantifying both anatomy and blood flow. Phase-contrast MRI (PCMRI) is a noninvasive method that can provide velocity data that are both spatially resolved across the vessel lumen and temporally resolved through the cardiac cycle. Briefly, the signal in MR images is a vector quantity, having both magnitude and phase. Motion in voxels while a bipolar gradient is applied results in an accumulation of phase proportional to the velocity in those voxels. Phase shifts of stationary tissue induced by system imperfections are offset while repeating the measurement with the bipolar pulse reversed and then subtracting the phase from the two acquisitions. A velocity image can be calculated from the phase image, and velocity values for each voxel can be integrated over the cross-sectional area of the vessel to derive volumetric flow measurements (27, 31). Because of limited techniques for data acquisition and analysis of PCMRI data from a large extent of vasculature, it is common to calculate spatial and temporal hemodynamic parameters by using the volumetric flow data derived from PCMRI as boundary conditions for computational fluid dynamics (CFD) simulations. These simulations are generally performed on discretized, 3D, geometric domains constructed from anatomic MRI data obtained from the same subject. The validity of calculated hemodynamic quantities along a complex geometric model using CFD simulations has been demonstrated (22). This combination of methods has been applied successfully clinically and in larger animal models (46) to provide insight into in vivo hemodynamic conditions. However, neither PCMRI, CFD, or the combination has been broadly applied to study in vivo blood flow in arteries of small animals.

The work presented here describes implementation, validation, and application of a through-plane PCMRI sequence on a 4.7-tesla small-bore scanner to quantify blood flow velocities through the infrarenal abdominal aorta of both rats and mice in vivo. Measurements of in vivo blood flow velocities were reproducibly acquired in a time-efficient manner. Derived volumetric flow rates were combined with geometric domains constructed from anatomic MRI data, acquired from the same animal, and used to perform CFD simulations to calculate WSS along the infrarenal aorta of rats and mice. Rodent data were compared with human imaging data and CFD results acquired using similar methods. An allometric law, consistent with recent theoretical predictions, relating WSS to body mass was obtained.

**MATERIALS AND METHODS**

All experiments were performed with local Institutional Animal Care and Use Committee approval in accordance with the institution’s ethical guidelines. Male 8- to 12-wk-old C57/BL6 mice (n = 5) and Sprague-Dawley rats (n = 5) were used.

*Velocity and anatomic MRI.* During all imaging, animals were anesthetized and maintained on 1–2% isoflurane in 1 l/min of oxygen. Body temperature was closely monitored and maintained at 37°C throughout imaging using warm air. Two subcutaneous electrocardiogram leads and a respiratory monitor (SA Instruments) were used for prospective triggering off of the R-wave during exhalation only. Threshold and blanking times were selected to avoid premature triggering. Imaging was performed at 4.7 tesla (Inova; Varian, Palo Alto, CA) using a 3- or 6-cm inner diameter, transmit-receive, radio frequency, volume coil (Morris Instruments, Ontario, Canada) to image mice and rats, respectively. An image acquired in the coronal plane was used to visualize the long axis of the aorta and subsequently prescribe slices perpendicular to the aorta for both blood flow velocity and anatomic MRI acquisitions described below.

To acquire spatially and temporally resolved in vivo velocity measurements, a prospectively triggered cine through-plane PCMRI sequence was implemented. The PCMRI sequence involved repeated measurements using reversed, bipolar, linear gradients [repetition time/echo time mouse: 8/4.2 ms, rat: 13/3.2 ms, field-of-view mouse: 3 cm², rat: 6 cm², matrix 128² zero filled to 256², slice thickness 2 mm, flip angle 20°, number of excitations = 8, 12 frames, velocity encoding value = 200 cm/s], resulting in a temporal resolution of 8 and 13 ms for mice and rats, respectively, and a total scan time of 2,048 cardiac periods. Velocity images were calculated after phase subtraction of the two acquisitions (Browser; Varian). In vitro validation of the PCMRI sequence included: 1) volumetric measurements at five steady flow velocities; 2) evaluation of the effect of non-steady-state acquisition resulting from prospective gating on measurement accuracy; 3) volumetric measurement of pulsatile flow with a period comparable to the rat’s cardiac cycle (~200 ms) and velocities near expected systolic and diastolic values in a rat aorta; and 4) determining the proper order of baseline corrections (0, 1st, or 2nd) needed to compensate for remaining phase errors after subtraction of the two acquisitions. All phantom studies used tubing with a diameter approximating a rat’s aorta (3 mm) and a calibrated in-line flow probe (Transonic Systems, Ithaca, NY) as the comparison metric. The boundary of the tube or aorta, over which velocities were integrated to obtain volumetric flow measurements, was manually defined using both magnitude and velocity images (MRvision, Winchester, MA). PCMRI data were used to compare velocity and volumetric flow values through the cardiac cycle between mice, rats, and humans. The Womersley (Wo) and mean Reynolds (Re) numbers reflecting the relative influence of transient inertial forces compared with viscous forces, were calculated for each animal using the following standard formulas: Re = ρvrd/µ, Wo = r(2πHRρµ)¹/², where ρ is density of blood (1.06 g/cm³), v is mean velocity, µ is the dynamic viscosity of blood (0.04 g·cm⁻¹·s⁻¹), d is the diameter of the vessel, r is the radius of the vessel, and HR is the heart rate. The PCMRI data were used as a noninvasively derived inlet boundary condition for subsequent CFD simulations.

To acquire geometric data of the aorta in vivo, a two-dimensional (2D) time-of-flight magnetic resonance angiography (TOF-MRA) sequence was used [repetition time/echo time 40/4 ms, field-of-view mouse: 3 cm², rat: 5.5 cm², matrix 256² zero-filled to 512², slice thickness 1 mm, no. of excitations = 4]. Contiguous slices were acquired starting just distal to the kidneys and extending ~7 mm
distal to the aortic bifurcation. A saturation pulse was placed distal to the acquisition slice to null the signal from venous blood and simplify segmentation of the aorta when constructing 3D geometric models to be used for CFD simulations. Typically, 21 and 37 slices were acquired in 15 and 25 min for mice and rats, respectively.

**Model construction and hemodynamic simulations.** 3D geometric models were constructed from the multislice 2D TOF-MRA data using custom software (52). Briefly, approximate centerline paths through the vessels of interest were defined. The image data were resampled in planes perpendicular to the centerline paths at user-defined locations and segmented by thresholding. The resulting 2D segmentations were smoothed spatially to eliminate high-frequency noise, and a solid model for each vessel was generated using a technique known as lofting. These solids were unioned (Boolean addition) to generate a single solid model representing the flow domain. The geometric model was discretized using a commercial meshing kernel (MeshSim; Simmetrix, Troy, NY). All rodent models were constructed by the same operator (Les). Geometric measurements of the infrarenal aorta were derived from the finished solid models. For CFD simulations, a Womersley analytic velocity profile was prescribed at the inlet, i.e., proximal infrarenal aorta, based on the data derived for each animal using the noninvasively acquired PCMRI data. Flow simulations were performed using resistance boundary conditions, calculated from the specific geometry of each model at the iliac and tail outlets and pressure values taken from the literature (17, 49). A stabilized finite element method was used to compute WSS from the incompressible unsteady Navier-Stokes equations assuming a Newtonian fluid with a viscosity of 0.04 g·cm⁻¹·s⁻¹ (47). No-slip boundary conditions were assigned at the wall, and rigid wall models were used in all simulations. Three maximum-element-edge-lengths (MEEL) (0.015, 0.010, and 0.007 cm), two time-step sizes (0.0005 and 0.001 s), and number of cardiac cycles (1, 2, or 4) were iteratively varied to compute and compare resultant WSS values along the length of one rat model to determine the appropriate values of each necessary to achieve convergence of computational solutions. Mean WSS along the infrarenal aorta was compared in mice, rats, and humans and used to evaluate the allometric scaling law relating WSS to body mass.

MR acquisition, model construction, and CFD simulations were performed in a similar manner for human data acquired by Tang et al. (45) and used in this study for comparison with rat and mouse data. Briefly, the extent of the aorta imaged and modeled was greater in humans (only results from the infrarenal aorta are used here); through-plane PCMRI measurements were acquired using retrospective cardiac gating, and 24 time points within the cardiac cycle were reconstructed; gadolinium-enhanced 3D MR angiograms were acquired for geometric information. All human models were constructed by the same operator (Tang).

**Statistical analysis.** Statistical analysis was performed using ANOVA followed by Scheffé’s post hoc analysis; a P value < 0.05 was considered significant. Linear regression was applied to log-log plots testing allometric relationships to determine the scaling exponent (b), a 95% confidence interval (CI) for the scaling exponent, and an R² value for the regression. Data are presented as means ± SE.

**RESULTS**

In vitro PCMRI data for validation had sufficient image quality to reliably define the boundary of the tube permitting proper integration of velocities over the tube cross section to derive accurate volumetric flow measurements (Fig. 1). The volumetric flow measurements made from PCMRI data acquired at five steady flow velocities showed excellent agreement with in-line flow probe measurements (R² = 0.96, slope = 1.1; Fig. 1A), and non-steady-state acquisition resulting from prospective gating did not effect the accuracy of these measurements (R² = 0.98, slope = 0.94; Fig. 1B). Although the first time point deviated from the flow probe measurement (most likely because of an inflow effect that was not observed in vivo), PCMRI measurements acquired in vitro using pulsatile flow with a period comparable to the rat’s cardiac cycle (~200 ms) were within 10% of Doppler flow probe values at every time point (Fig. 1C). The PCMRI images spanned an acquisition time slightly less than the period of the flow phantom, resulting in the last flow probe data point not having a counterpart. This was done to mimic in vivo implementation where variations in the length of the cardiac cycle might be
anticipated. As expected, this did not result in a large difference between the mean flow rates (433 and 422 ml/min for the flow probe and PCMRI, respectively).

In vivo images are displayed using standard radiological conventions (the left side of the subject is displayed on the right side of the image, and anterior is at the top of the image). Although image quality was comparable to in vitro data, initial in vivo scans revealed the need to assign the readout direction left-right rather than anterior-posterior during data acquisition to minimize the deleterious effect of chemical shift artifact (from abdominal fat) on properly defining the boundary of the aorta. Having made this change, through-plane PCMRI data were successfully acquired for all mice and rats with an approximate acquisition time of 10 min/animal. A magnitude and velocity image from PCMRI acquisitions for a representative mouse and rat, along with an anatomical image taken at approximately the same position along the aorta using the 2D TOF-MRA method (note the successful suppression of signal in the vena cava), are displayed in Fig. 2A. Signal from the vena cava was successfully saturated in both species and expedited image segmentation during CFD model construction. The imaging parameters used resulted in five to six and six to seven voxels across the vessel lumen for mice and rats, respectively. Velocities at approximately peak systole resolved across the vessel lumen, from a representative mouse and rat, and qualitative demonstration of reproducibly measuring volu-

![Figure 2A](image-url)  
**Fig. 2. In vivo application.** A: representative anatomic images from the 2-dimensional (2D) time-of-flight magnetic resonance imaging (TOF-MRA) sequence and magnitude and velocity images from the PCMRI sequence (arrow, aorta; arrowhead, vena cava). Signal from the vena cava was successfully eliminated in the anatomic images. B: representative plots of velocity across the lumen at approximately peak systole for both species. Horizontal axes are in voxels. In-plane voxel dimensions for mice and rats, respectively, were 0.0117 and 0.0234 cm. C: volumetric measurements calculated from velocity images are displayed for every animal and demonstrate that PCMRI measurements were reproducible between animals. The waveforms corresponding to the plots in B are represented by a dashed line with the arrow indicating the image number from which the systolic velocity plots were derived. n, No. of experiments.
metric flow through the cardiac cycle in the proximal infrarenal aorta of both species are shown in Fig. 2, B and C, respectively. The maximum velocities ($V_{\text{max}}$) for the mouse and rat data in Fig. 2B were 64 and 134 cm/s, respectively. Estimating the flow rate at this time point by using the equation $\frac{1}{2}(V_{\text{max}})(60)(\pi)(\text{radius})^2$ with the mean diameter for the given mouse and rat equal to 0.07 and 0.16 cm, respectively, results in values within 25% of measured quantities (Fig. 2C), which is reasonable given the assumption of parabolic flow for the equation. In vitro and in vivo data were used to determine that a first-order (i.e., linear) baseline correction best rectified remaining static phase errors in both mouse and rat data; resulting velocities in static tissue averaged less than $\pm$2 cm/s (data not shown). This analysis was of particular importance because of the inability to use static regions in the area ventral to the aorta because of ubiquitous phase artifacts associated with the digestive tract. For comparison, Fig. 3 shows mean velocities, averaged across the vessel lumen, plotted against time normalized to the mean period of the respective species’ cardiac cycle (mouse: 0.119 ± 0.01, rat: 0.167 ± 0.01, human: 1.07 ± 0.05 s; corresponding to heart rates in beats/min of 504, 359, and 56). Mean velocities did not consistently increase with species’ size (mouse: 11.9 ± 0.8, rat: 32.5 ± 1.8, human: 10.8 ± 1.0 cm/s). Plots of volumetric flow rates through the cardiac cycle for each species required individual plots (Fig. 4, A–C). Mean flow rates for mice, rats, and humans were 2.8 ± 0.1, 35.7 ± 1.9, and 856.5 ± 128 ml/min. Womersley (mouse: 1.4 ± 0.05, rat: 2.7 ± 0.07, human: 7.6 ± 0.5) and mean Reynolds (mouse: 22.8 ± 1.8, rat: 143.8 ± 9.9, human: 367.6 ± 40.2) numbers were directly related to species’ size.

The 2D TOF-MRA data were successfully reconstructed into 3D geometric models for all mice and rats. CFD tests for mesh independence showed that differences in WSS values, along the entire extent of the model, were most affected by the MEEL rather than time step or number of cardiac cycles. The difference in WSS values from simulations run with an MEEL of 0.010 and 0.007 cm averaged <10%. Therefore, an MEEL of 0.005 cm for mice and 0.010 cm for rats (resulting in an average no. of elements/model of 548,737 ± 19,000 and 782,083 ± 54,000, respectively) was prescribed. A time step of 0.001 s and three cardiac cycles were used for both species. Representative computational models displaying mean WSS values, averaged over a single cardiac cycle, along the infrarenal aorta for each species are displayed in Fig. 5. Of qualitative note, all mouse and rat models showed areas of low WSS at the lateral walls of the aortic bifurcation; most also showed an area of high WSS on the anterior surface of the midaorta that appeared to be related to slight anterior-posterior curvature.

![Fig. 3](http://ajpheart.physiology.org/) Plots of mean velocity averaged across animals for each species. Velocity ranges across species were similar enough to plot on the same scale. The abscissa is the time ($t$) normalized to the mean period of the respective species’ cardiac cycle (T); mouse: 0.119, rat: 0.167, and human: 1.07 s.

![Fig. 4](http://ajpheart.physiology.org/) Comparison of mean volumetric flow plots across species. Volumetric flow rates differed substantially and are plotted with axes appropriate for each species. A: mouse; B: rat; C: human. Peak volumetric flow differed by an order of magnitude between mice and rats as well as between rats and humans.
in this region. The average diameter along the aorta (0.07 ± 0.001, 0.17 ± 0.006, and 1.3 ± 0.09 cm) and the average vertical length (0.7 ± 0.008, 1.7 ± 0.002, and 7.9 ± 0.5 cm) over which WSS was averaged for mice, rats, and humans are included for comparison of vessel geometry. The longitudinal extent for the mice and rats began −0.3 and 0.5 cm below the inlet of the model and ended just above the aortic bifurcation, avoiding inclusion of WSS variations resulting from inlet effects or branching, respectively. The former precaution was not needed in human data sets since the models began farther proximally. Mean WSS, averaged over the surface area of the infrarenal aorta, was significantly greater in mice and rats compared with humans (87.6 ± 8.3, 70.5 ± 6.7, 4.8 ± 0.3 dynes/cm², P < 0.01; Fig. 6A) and showed an inverse relationship to body mass (mouse: 23 ± 0.6, rat: 308 ± 14, human: 67,860 ± 3,620 g). Using linear regression to fit a log-log plot of WSS and body mass, the noninvasively derived in vivo measurements presented here predict a scaling exponent of $b = -0.38$ ($R^2 = 0.92$; Fig. 6B). Included in the plot (Fig. 6B) is an estimation for WSS in the canine abdominal aorta derived from Chandran et al. (1). Mean shear rates across the cardiac cycle for rodent and human data ranged from 48 to 1,689 s⁻¹.

Allometric comparisons of other geometric and hemodynamic quantities mentioned above were carried out as well. The resulting scaling exponents ($b$), 95% CI for $b$, measures of quality of fit for the data ($R^2$), and comparison with previously published values are shown in Table 1.

**DISCUSSION**

We have successfully implemented a 2D through-plane PCMRI sequence to acquire temporally and spatially resolved blood flow velocities in vivo in mice and rats. We were able to combine this data with geometric information from the same animal, obtained using a 2D TOF-MRA method, and perform CFD simulations to calculate WSS along the infrarenal aorta of mice and rats.
Table 1. Summary and comparison with literature values of geometric and hemodynamic parameters for which allometric laws were calculated

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Slope (b)</th>
<th>R²</th>
<th>95% CI</th>
<th>Previously Reported Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radius</td>
<td>0.36</td>
<td>0.99</td>
<td>0.35 to 0.38</td>
<td>0.375 (8, 40, 51)</td>
</tr>
<tr>
<td>Flow</td>
<td>0.69</td>
<td>0.98</td>
<td>0.63 to 0.75</td>
<td>0.75 (8, 40, 51)</td>
</tr>
<tr>
<td>Mean Velocity</td>
<td>−0.04</td>
<td>0.07</td>
<td>−0.13 to 0.05</td>
<td>−0.05, 0.0 (40, 51)</td>
</tr>
<tr>
<td>Mean Re</td>
<td>0.32</td>
<td>0.84</td>
<td>0.24 to 0.41</td>
<td>0.34 (40)</td>
</tr>
<tr>
<td>Wo</td>
<td>0.21</td>
<td>0.98</td>
<td>0.19 to 0.23</td>
<td>0.25 (51)</td>
</tr>
<tr>
<td>WSS</td>
<td>−0.38</td>
<td>0.92</td>
<td>−0.45 to −0.31</td>
<td>−0.2, −0.375 (23, 51)</td>
</tr>
</tbody>
</table>

Re, Reynolds no.; Wo, Womersley no.; WSS, wall shear stress; b, scaling component; CI, confidence interval. Ref. nos. are in parentheses.

In implementing the PCMRI sequence for customary use in small animal models, where small geometry and rapid heart rates can be challenging, we were able to fulfill many of the criteria known to affect measurement error (27). Triggering the acquisition off of the R wave only during expiration mitigated pulsation artifacts that can contribute to spatial misregistration and lead to difficulty in correctly defining the border of the vessel; spatial resolution obtained in these studies resulted in five to seven voxels across the lumen in both species; and the imaging plane for PCMRI acquisitions was not likely to be more than a few degrees away from perpendicular because of prescribing slices from a coronal image that visualized the longitudinal direction of the aorta, and all aortas appeared circular rather than ovoid. The aspect ratio of the voxels may need to be improved in future work. Presently, this could have led to partial volume effects that would be exacerbated by deviations of the imaging plane from perpendicular, resulting in an underestimation in velocities. Setting a velocity encoding value of 200 cm/s, to avoid velocity aliasing, was appropriate for rats but perhaps too high for mice. The number of frames acquired per cardiac cycle may need to be increased for mice to more appropriately match the rapid heart rates and to accurately evaluate whether there is retrograde flow in either rodent species.

In summary, the potential limitations of the PCMRI technique in this work tend toward an underestimation of velocity and flow measurements. Therefore, true WSS values in mice and rats may be even greater than presented here. This would lead to a larger negative slope in the log-log plot of WSS and body mass (Fig. 6B); however, −75% larger WSS values in rodents (and therefore approximately equivalent increases in mean flow values) would be necessary to predict a scaling exponent outside the 95% CI of the work presented here (−0.45 to −0.31). Although isoflurane has been shown to be the anesthetic of choice for measurements of systemic hemodynamics (6, 16, 19) and heart rates during imaging were comparable to what others have shown for 1 and 1.3% isoflurane in mice and rats (6, 16), heart rates (as is typical for isoflurane) were still 24–31% and 7–11% below values published for conscious mice and rats, respectively (6, 16, 19). If one assumes a linear increase in mean flow rate with increasing heart rate, this would account for less than one-half of the necessary 75% increase in rodent WSS values mentioned above with the remaining error to be derived from the PCMRI and CFD methods themselves. Again, with the agreement of mean blood flow velocity, flow rates, and geometry to values published previously by others, such a large error in the imaging and computational techniques may be unlikely.

WSS values calculated from the combination of PCMRI, 2D TOF-MRA, and CFD simulations were inversely related to body size as predicted by Langille (23), who notes that this relationship has been overlooked because of an “unfortunate consensus” that we suspect persists today, i.e., that mean WSS in large arteries is invariant across species. WSS values presented here are one to five times greater than those previously presented for mice (16–49 dyn/cm²; see Refs. 14, 23, and 43) and rats (25–55 dyn/cm²; see Refs. 23 and 42), most likely being a direct reflection of the noninvasive method used to acquire flow data. Specifically, we determined a scaling exponent for WSS of $b = -0.38$ (95% CI $-0.45$ to $-0.31$), significantly different from that originally proposed by Langille. Langille’s original estimate of $b = -0.2$ was derived using literature values of allometric scaling exponents for flow ($b = 0.8$) and radius ($b = 0.33$) in combination with the equation for
mean shear stress obtained from solving the Navier-Stokes equations for Poiseuille flow, $\tau = 4\mu Q/r^3$, where $\mu$ is viscosity of blood, $Q$ is volumetric flow, and $r$ is radius (23). Although a very perceptive contribution to better understanding how WSS varies across species, the choice of using the scaling exponent for radius associated with principles of geometric similarity rather than elastic similarity (8, 40) led to an underestimation. If instead the scaling exponent for radius derived from considerations of elastic similarity is used, $b = 0.375$, a scaling exponent of $b = -0.325$ is calculated for WSS and is not significantly different from the one measured in the present work. Furthermore, if the scaling exponent of $b = 0.75$ (now generally accepted for parameters like blood flow which are directly related to organismal metabolic demand; see Refs. 40 and 51) is used, the scaling exponent calculated for WSS is $b = -0.375$, identical to that which we determined experimentally in this work using noninvasive in vivo and in silico techniques. Although we could have used Langille’s approach, i.e., use values of the scaling exponent for blood flow and radius (as calculated from PCMRI and 2D TOF-MRA data, respectively) along with $\tau = 4\mu Q/r^3$, to arrive at the same answer for the scaling exponent of WSS (actually $b = -0.39$), in future studies we hope to use the CFD simulations to provide spatially and temporally resolved information about WSS along the aorta rather than averaging over an extent of vessel. It is reassuring, however, to see that we have empirically demonstrated the allometric law for WSS, using PCMRI and CFD simulations, that would be predicted from more thoroughly studied parameters such as blood flow and radius. The agreement of data from a fourth species (canine; Fig. 6B), as recommended by others (26), provides confidence that the allometric fit is reliable. Although the use of branching exponents as a way to predict shear stress in the vascular tree has long been proposed, others have demonstrated that a heterogeneous distribution of branching exponents, as occurs in vivo, results in the shear stress distribution being nearly independent of the branching exponent (18). This suggests that WSS needs to be measured directly rather than inferred, with the presented methodology providing a step in that direction.

Although it might be enticing to initially focus on the regions of low WSS along the lateral hips of the aortic bifurcation that were present in all of the rodent models (and which correspond to an 80% localization rate of atherosclerotic lesions in this area in a murine model of familial hypercholesterolemia; see Ref. 35 and Greve, unpublished observations), previous work by Moore et al. (29) suggests that further work will be required to better understand the errors associated with geometric reconstruction from in vivo MRI data in this region and how they might be exacerbated in the smaller geometry of rodent models before using PCMRI and CFD to study this location. In juxtaposition, they demonstrated that the extent of the infrarenal aorta proximal to this area was reconstructed with higher fidelity (29). Therefore, the PCMRI and CFD methods presented here could be appropriately utilized to serially quantify flow field characteristics during disease progression or therapeutic intervention in small animal models of cardiovascular disease affecting this extent. Of particular interest would be models of abdominal aortic aneurysm where it has already been shown in experimental studies (42) that flow conditions affect cellular inflammation and that, clinically, inflammation is correlated to aneurysm size (9), with the limitation of the current data being that it is a single time point for a given subject and not spatially related to local hemodynamic conditions. The assumption of a Newtonian fluid was justified for the data from normal aortas presented here, as evidenced by the shear rates, but may need to be reconsidered in disease states along with the possible advantages of incorporating a deformable wall algorithm to account for vessel wall compliance.

The iliac and aortic disease states mentioned above highlight the potential utility of the noninvasive methodology developed here to study hemodynamics in relation to pathophysiology in both a temporally and spatially resolved manner and allow serial investigation in experimental models over the course of disease development or therapeutic treatment. With the ability to visualize inflammation in vivo using iron oxide particles and MRI, as has been done to study atherosclerosis in animal models and humans (21, 39), the presented methodology holds the potential to elucidate the relationship between flow field characteristics and vascular disease on both macroscopic and microscopic scales [as defined by Friedman and Giddens (10)]. It could achieve the ideal combination of obtaining hemodynamic information and vessel response in the same vessel (10).

Finally, but not insignificantly, it is interesting to consider that allometry (besides that related to pharmacokinetics or -dynamics) has rarely been considered when trying to understand the success or failure of a therapeutic intervention (3). The present work may be worthy of reflection in this regard.

ACKNOWLEDGMENTS

We gratefully acknowledge C. Alberto Figueroa for providing assistance with the computer simulations.

GRANTS

This research was supported by National Science Foundation under Grant 0205741, by National Institutes of Health Grants R01HL-064338 and P41RR-09784, and the Lucas Foundation.

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