Twenty-fold difference in hemodynamic wall shear stress between murine and human aortas

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Abstract

Endothelial cells regulate vascular tone and mural remodelling in a shear-dependent manner that is commonly assumed to keep wall shear stress constant across arteries and species. Allometric arguments show that aortic flow velocity is constant across species, a deduction that is consistent with much experimental data, but the same arguments also show that the shear stress experienced by aortic endothelium will depend inversely on body mass to the \( \frac{3}{8} \)th power, and hence will be 20-fold higher in mice than in men. This conclusion is robust and has important implications for the study of shear-dependent vascular biology and pathology.

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1. Introduction

Endothelial cells are sensitive to the shear stress (frictional force per unit area) imposed on them by the flow of blood. Although it is not well understood how stress is sensed, cell membrane proteins and the cytoskeleton are involved, and shear stress affects membrane and cytoskeletal properties, turnover, receptor expression, cell signalling and gene expression, (e.g., Davies et al., 2002; Li et al., 2005). The shear-dependence of endothelial behaviour has consequences for the homeostatic regulation of thrombosis, vessel diameter, wall permeability, inflammation and angiogenesis, as well as for the development of atherosclerosis.

It is widely believed, (e.g., Smiesko and Johnson, 1993; Kamiya and Togawa, 1980; Zarins et al., 1987; Tronc et al., 1996), that across many arteries and species, endothelial cells control vessel diameter through wall remodelling and smooth muscle tone to keep the mean shear stress they experience at around 10–15 dynes/cm\(^2\). It is clear, however, that shear stress is not uniform in areas of arterial curvature and branching; indeed this variation is commonly assumed to underlie the patchy nature of atherosclerosis (Caro et al., 1971; Ku et al., 1985). Furthermore, substantial differences in shear stress occur between arteries within an individual (Ethier et al., 1999; Dammers et al., 2003; Wu et al., 2004). Here we show from more detailed and accurate scaling arguments than previously presented (Westerhof et al., 2005; Les et al., 2005), and from reference to physiological measurements in the literature, that aortic wall shear stress must vary appreciably between species, most likely with an inverse \( \frac{3}{8} \)th power dependence on body mass.

2. Allometry

We first consider the scaling of key cardiac parameters. For mammalian species, there is substantial evidence, (e.g., Prothero, 1979), that cardiac mass varies in direct proportion to body mass; it is “isometric”. This suggests that ventricular stroke volume should also scale with body mass, which is precisely what is observed (Holt et al., 1968). Many other features of the cardiovascular system, however, are allometric. The interval between heart beats, for
example, is not directly proportional to body mass but follows a quarter power law (Stahl, 1967):

\[ f_h \propto M_b^{0.75} \tag{1} \]

where \( f_h \) is heart beat frequency, \( M_b \) is body mass and \( c = -0.25 \) is the so-called body-mass exponent (see Table 1).

The product of the relations for stroke volume and heart rate suggests that cardiac output should vary approximately as \( M_b^{0.75} \). An exponent of 0.75 is also expected on theoretical grounds (West et al., 1997) and because of the large quantity of data showing that metabolic rate is proportional to \( M_b^{0.75} \)—the classical “mouse-to-elephant curve” (Kleiber, 1932; Brody et al., 1934). Empirical observations are in close agreement with this prediction. Stahl (1967), for example, obtained an exponent of 0.81 (95% confidence interval of \( \pm 0.01 \), correlation coefficient \( r = 0.98, n = 568 \)) while Holt et al. (1968) obtained 0.79 (\( +0.06, r = 0.97, n = 43 \)).

Not all organs scale in size like the heart (Schmidt-Nielsen, 1984). Although some authors have assumed that aortic diameter and cross-sectional area are isometric, experimental data do not support this supposition. Clark (1927) obtained a body-mass exponent of 0.82 (95% confidence interval \( \pm 0.03 \)) for aortic cross-sectional area in 35 mammalian species and Holt et al. (1981) obtained 0.36 \( \pm 0.02 \) for aortic diameter (equivalent to 0.72 for area). Here we assume a body-mass exponent of 0.75 for area, which lies approximately midway between these results and is predicted on theoretical grounds (West et al., 1997).

Combining the assumptions for cardiac output and aortic cross-sectional area leads to an exponent of zero for the mean flow velocity, i.e. aortic blood velocity is predicted to be constant across species. (Schmidt-Nielsen (1984) uses different scaling arguments to deduce an exponent of \(-0.07\), which is for practical purposes indistinguishable from the value of zero proposed here.) Measurements for species of disparate size do indeed show similar aortic blood flow velocities, consonant with this deduction and with the validity of the allometric approach in general. For example, Doppler ultrasound studies give average peak velocities for the aortic root of 1.04 m/s in mice (Lacy et al., 2001) and 1.03 m/s in men (Khir et al., 2001), despite \( M_b \) differing by >3 orders of magnitude. At minimum, such results demonstrate that aortic cross-sectional area and cardiac output must have essentially the same body-mass exponent.

Allometric rules for a number of non-dimensional hemodynamic groups can be deduced along similar lines. For example, aortic Reynolds number (Re), a measure of the relative significance of inertial and viscous forces, is predicted to scale with a body-mass exponent of 0.375, since the kinematic viscosity of blood is approximately invariant between species (Li, 1996). (Schmidt-Nielsen (1984) deduces 0.34.) The aortic Womersley parameter, a dimensionless measure of flow unsteadiness, and the entrance length, indicating the distance before fully-developed flow is established after a hemodynamic perturbation, should have exponents of 0.25 and 0.75, respectively.

Of particular importance for endothelial behaviour is the result that, given a size-invariant aortic flow velocity and blood viscosity, and a body-mass exponent of 0.375 for aortic diameter, the cardiac cycle-averaged shear stress at the aortic blood-wall interface (i.e., the product of the velocity gradient and viscosity) is predicted to scale with a body-mass exponent of \(-0.375\). Assuming typical body masses of 25 g, 3.5 kg and 75 kg for mice, rabbits and people, the shear stresses for these species should therefore be in the approximate ratios 20:3:1, respectively. Whilst there would be little surprise at the conclusion that Re scales in the opposite fashion—giving entirely conventional values of, say, 500 in rabbits and 1500 in people—the necessary corollary that shear stress differs by such a wide margin across species is contrary to current orthodoxy.

### 3. Sensitivity to aortic diameter

How robust is this conclusion? For a given cardiac output, wall shear stress depends on diameter cubed, and hence these arguments are potentially most sensitive to errors in assessment of diameter. However, the in vivo data cited above show that aortic velocities are the same across species of disparate size, as theoretically predicted. For a known velocity, wall shear stress depends only on the first power of diameter, and hence is much less sensitive to measurement errors. Nonetheless, it is still worth inquiring whether errors in diameter measurements could invalidate our conclusion. The diameter measurements of Clark (1927) were obtained post mortem, in the absence of pressure. Those of Holt et al. (1981) were obtained from pressure casts of the aortas, but even with this technique there is an absence of flow, which removes one of the factors regulating diameter. There have been no studies of aortic diameter across a wide range of species under physiological or near-physiological conditions, but spora-

<table>
<thead>
<tr>
<th>Hemodynamic parameter</th>
<th>Body-mass exponent, ( c )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac output</td>
<td>0.75</td>
</tr>
<tr>
<td>Heart rate</td>
<td>(-0.25)</td>
</tr>
<tr>
<td>Aortic diameter</td>
<td>0.375</td>
</tr>
<tr>
<td>Mean aortic blood velocity *</td>
<td>0</td>
</tr>
<tr>
<td>Aortic Reynolds number *</td>
<td>0.375</td>
</tr>
<tr>
<td>Aortic Womersley parameter *</td>
<td>0.25</td>
</tr>
<tr>
<td>Aortic entrance length*</td>
<td>0.75</td>
</tr>
<tr>
<td>Cycle-averaged aortic wall shear stress *</td>
<td>0.375</td>
</tr>
<tr>
<td>Temporal gradient of aortic wall shear stress *</td>
<td>-0.625</td>
</tr>
</tbody>
</table>

Body-mass exponent, \( c \), is defined in Eq. (1). Quantities marked with an asterisk are derived from body-mass exponents for the first three entries in the table. The first three entries are based on literature values as described in the text.
4. Spatial and temporal variations in shear

So far only cycle-averaged wall shear stresses have been considered; however, there is evidence that endothelial cells are also sensitive to temporal gradients in wall shear stress (Bao et al., 1999, 2000). To make statements about temporal variations in wall shear stress we need to know how the flow waveform (cardiac output as a function of time) depends on body mass. Surprisingly, resting velocity waveforms in the ascending aorta are remarkably similar across a wide range of species, after adjustment for the different periods (Nichols and O’Rourke, 1990). Assuming a flow waveform shape that is independent of body mass, temporal gradients of shear stress are expected to scale with a body-mass exponent of approximately $-0.625$, i.e. in the ratio $150:7:1$ in mice, rabbits and humans. (This scaling is not quite exact, since temporal gradients in shear scale nonlinearly with Womersley parameter, but for the range of Womersley parameters expected in mammals we can ignore this effect as second-order.) Hence the dependence of the temporal gradient of wall shear stress on body mass is predicted to be even more severe than the dependence of cycle-averaged wall shear stress. It is also noteworthy that if the shape of the flow waveform is relatively independent of body mass, the maximum value of wall shear stress over the cardiac cycle will scale approximately in the same way as cycle-averaged wall shear stress.

Another complicating factor is the possibility of interspecies differences in blood velocity profiles. The exact shape of the velocity profile at any location depends on many factors; near the aortic root the velocity profile leaving the left ventricle is somewhat blunt, becoming more developed further downstream, so that the velocity profile in at least the ascending aorta depends on entrance length. However, a more important factor is the curvature of the aorta, which induces secondary flows that depend on Reynolds number in a complex manner (e.g., Chandran, 1993). The shear stress effects of such secondary flows are not amenable to prediction from simple scaling arguments. However, they provide only local modulation about a mean shear stress value; in other words, they will affect the spatial variation and distribution of shear, but not the fundamental relation of its mean value to body mass described above.

5. Conclusions

Allometry does not generate precise laws, only general trends. Race horses and cattle have similar body masses but the demands on their circulatory systems are different. In addition to such “biological noise” (Schmidt-Nielsen, 1984), there are clear exceptions to some of the rules. For example, heart rates in shrews ($M_b \sim 3$ g) are substantially lower than predicted, perhaps because the short inter-beat interval ($\sim 20$ ms at maximum heart rate) calculated from the allometric rule is incompatible with conduction velocities and muscle contraction rates (Schmidt-Nielsen, 1984). Nevertheless, our general conclusions appear robust. In particular, because of the allometric arguments and physiological data demonstrating that aortic flow velocity is constant across species, the only assumption that does not give increasing wall shear stress with decreasing body mass is the patently absurd one that aortic diameter remains the same or increases with decreasing body size. Shear stresses an order of magnitude lower than the generally expected $10–15$ dyn/cm$^2$ have recently measured in the human descending aorta by Cheng et al. (2003a, b). Additionally, there are decreases in carotid artery shear stress with increasing body mass: $35$ dynes/cm$^2$ in mice (Castier et al., 2005), $19–29$ dynes/cm$^2$ in rats (Ibrahim et al., 2003), $9–17$ dynes/cm$^2$ in rabbits (Di Stefano et al., 1998) and $7$ dynes/cm$^2$ in people (Hoeks et al., 1995). These data, obtained by diverse methods, do not conform to a body-mass exponent of $-0.375$, but this value was calculated for the aorta; exponents may differ between arteries as they do between organs. The data are consistent with our general argument that shear will strongly depend on size. Whilst the present paper was being reviewed, Greve et al. (2006) published wall shear stresses for the abdominal aorta of mice, rats, dogs and people. Their values, derived from MRI data, give a best fit body-mass exponent of $-0.38$. The remarkable agreement with our prediction of $-0.375$ suggests that the arguments presented above are not just generally correct but quantitatively accurate as well.

Allometric relations exist within species as well as between them. Intra-species rules tend to be similar to inter-species ones, although exponents may differ slightly (e.g., Heusner, 1982). Consistent with the trend we have predicted, wall shear stress declines significantly with maturation (and hence size) in the rabbit carotid artery (Di Stefano et al., 1998). Such intra-specific allometric relations might help explain the change in distribution of atherosclerotic lesions that occurs with age in rabbit and human aortas (Weinberg, 2002, 2004).

Our central conclusion is that mean aortic shear stress must differ substantially between species of different size; most importantly, the mouse, a widely-used model of disease, should have 20-fold higher aortic wall shear stress...
(and 150-fold higher temporal shear gradients) than people. This conclusion raises several fundamental questions about endothelial cell biology. Is endothelial responsiveness adjusted by some unknown mechanism to the shear experienced in each species, resulting in similar biological properties, or is endothelial responsiveness to shear essentially constant across species, resulting in size-dependent endothelial phenotypes? Are blood cells also affected? What are the implications for animal models of human disease, particularly murine models, given the large disparity in wall shear stress between species and the important role that shear plays in atherogenesis? Comparative studies are required for a proper understanding of endothelial responses to shear stress in healthy and diseased human arteries.

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References


