

Hemodynamic Influences on Abdominal Aortic Aneurysm Disease

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The term "hemodynamic forces" refers to the kinetic energy generated by the flow of blood through arteries and veins. Vascular endothelial and smooth muscle cells are constantly exposed to a variety of physical stimuli generated by flowing blood. Two parameters relevant to abdominal aortic aneurysm (AAA) pathogenesis include the tangential force exerted by moving blood along the axis of flow (**wall shear stress (WSS)**) and the motion exerted by cyclic luminal pressure changes on aortic diameter (**relative wall strain (RWS)**). Under normal homeostatic conditions arteries regulate diameter in part due to WSS sensed and transduced via endothelial cells¹⁻⁴. Growing experimental evidence indicates that low antegrade or oscillatory shear conditions promote proliferative, thrombotic, adhesive and inflammation-mediated degenerative conditions throughout the vascular system⁵. Although aneurysm enlargement and rupture are a function of both aortic structural integrity and hemodynamic forces, most AAA research to date has focused on degenerative mechanisms within the aortic wall⁶⁻⁷ and epidemiological risk factors⁸ rather than on the influence of intraluminal physical forces on disease progression⁹.

Several clinical situations highlight the potential influence of hemodynamic forces on AAA pathogenesis. Post-traumatic above knee amputees were found to be 5 times more likely to develop AAA > 40 years following injury than non-amputee subjects matched for traditional AAA risk factors such as cigarette smoking. Aneurysm morphology in the amputee patients was strongly influenced by amputation laterality, prompting the original observation that chronically diminished or asymmetric distal aortic blood flow promotes and mediates aneurysmal aortic degeneration (**Figure 1**)¹⁰.

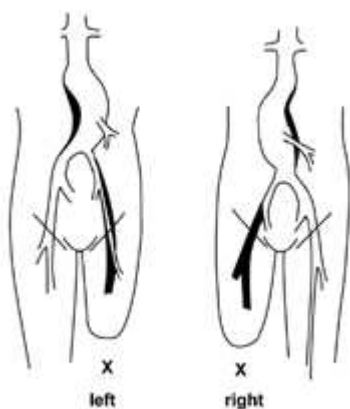


Figure 1. (Vollmar et al., ref 10)



Spinal cord injury (SCI) patients also appear to be at > 2 fold risk for AAA formation more than two decades following injury as compared to age and risk-factor matched ambulatory control subjects. In SCI patients high resting peripheral resistance greatly diminishes distal aortic and iliac blood flow, generating chronically low antegrade and oscillatory shear stress conditions in the infrarenal abdominal aorta¹¹. The presence of small or diseased distal arteries may also predispose ambulatory, bipedal patients to develop AAA disease. Excluding patient with popliteal or femoral aneurysms, distal arterial diameters are smaller than average in AAA patients¹². This finding 1) discounts the likelihood of a general arterial dilating diathesis as a predisposing condition in most AAA patients and 2) provides further support for a putative etiologic connection between

sedentary existence (as evidenced by diminished distal arterial diameter) and increased AAA risk. A recent report of the SMART study group confirmed multiple previous observations noting increased AAA risk in patients with symptomatic peripheral vascular disease¹³. While this predilection for AAA in PVD patients may be due in part to the common influence of shared risk factors (such as cigarette smoking) for both diseases, it is also likely that symptomatic PVD results in reduced lower extremity exercise,

promoting low antegrade and oscillatory shear forces in the infrarenal aorta and eventual aneurysmal degeneration.

Turbulence, vibratory forces and transmural pressure gradients (hypertension) are also hemodynamic influences relevant to AAA pathogenesis and progression. Turbulence and vibratory forces are difficult to measure in-vivo and hence less well described. The presence of hypertension, although previously associated with increased risk for AAA rupture¹⁴⁻¹⁵ is not so clearly associated with increased risk for developing AAA disease. The largest and most comprehensive prevalence and association study completed to date did not identify hypertension as an independent risk factor for AAA disease⁸. In experimental animal models selective inducible nitric oxide synthase (iNOS) inhibition induces hypertension while paradoxically limiting AAA progression¹⁶. While pressure clearly influences rupture risk, hypertension may not predispose patients to aneurysmal degeneration at earlier timepoints in the course of their disease.

Animal AAA models provide unique opportunities for examining the influence of hemodynamic forces such as WSS and RWS on aneurysm pathogenesis. Quantifying wall shear and strain forces requires the simultaneous measurement of blood pressure, blood flow, and cyclical wall motion. These three parameters are measured in rodent models using intraluminal pressure transducer catheters (Millar Micro-tip; Millar Instruments, Houston, TX), ultrasonic flow probes (Transonic Systems Inc, Ithaca, NY), and ultrasound microcrystals for diameter measurement via triangulation (Sonometrics Sonosystem® London, Ontario). Wall motion or cyclic wall deformation may also be measured accurately using high-speed video microscopy (> 30 frames/second). WSS is calculated as $4 \times 0.035 \times Q / \pi r^3$ (Poiseuille's law) where 0.035 is blood viscosity in poise, Q = mean blood flow, and r = aortic radius. Relative wall strain is calculated as (max diameter - minimum diameter) / minimum diameter.

Intra-aortic elastase infusion reliably produces AAA in mice and rats. This is the best-described and most widely used method of experimental aneurysm formation¹⁷. Immediately following a two-hour infusion period, histological analysis demonstrates fragmented and disorganized elastic lamellae. Within 12 hours no stainable elastic lamellae remain. Collagen remains present and apparently unaffected in the immediate post-infusion interval. Within the first 48 hours, only minimal (<25%) aortic diameter enlargement is noted. Beginning on the second post-infusion day, infiltrative mono- and polynuclear inflammatory cells are noted in the media and adventitia. Both the degree of elastin degradation and the intensity of the ensuing inflammatory infiltrate correlate with the rapidity and extent of aneurysmal aortic enlargement. Within 14 days AAA develop and aortic diameter increases > 4 fold. Elastin degradation and the formation of elastin degradation peptides (EDPs) promote strong chemotactic responses from macrophages, and may represent the initial pro-inflammatory stimulus in human aortic aneurysms⁶. AAA pathogenesis in the elastase infusion models has been partially defined through a series of inhibition experiments using hydroxamic acid compounds (for selective and non-selective matrix metalloproteinase (MMP) inhibition), indomethacin, selective iNOS inhibitors, anti-CD 18 monoclonal antibodies and genetically deficient mice¹⁸⁻²².

We have created distal femoral arteriovenous fistulae (AVF) or employed distal iliac ligation to modify aortic blood flow, WSS and RWS in rodent models²³⁻²⁴. Small distal AVF do not measurably influence arterial pressure, but do increase flow, shear and strain forces as noted below (**Table I, AVF = <3mm femoral avf, Sham = sham femoral exposure, *= significantly different from sham at the 0.05 level**)

GROUPS	Flow (ml/min)	Wall Shear Stress (dynes/cm ²)	Diameter (mm)	Wall Strain (%)
3 day AVF	34 ± 13*	4.0 ± 1.3*	1.7 ± 1.0*	9.0 ± 2.8*
3 day SHAM	16 ± 6	2.9 ± 0.7	1.5 ± 1.1	5.4 ± 1.0
7 day AVF	40 ± 10*	3.3 ± 1.7	2.0 ± 0.3	8.7 ± 4.0
7 day SHAM	15 ± 6	2.7 ± 1.6	1.5 ± 0.2	6.71 ± 2.3
21 day AVF	49 ± 21*	2.7 ± 1.2	2.2 ± 0.4*	11.9 ± 5.6
21 day SHAM	10 ± 5	1.2 ± 0.5	1.6 ± 0.4	8.7 ± 3.6

Flow mediated arterial enlargement is dependant upon vascular smooth-muscle cell mediated extracellular matrix remodeling (MMP-2 and possibly MMP-9 activity)²⁴⁻²⁵, disruption and reformation of the internal elastic lamina²⁶ as well as endothelial cell migration and proliferation²⁷.

We have employed both distal arteriovenous fistula creation and iliac ligation to examine the influences of WSS and RWS on AAA pathogenesis in the rodent elastase infusion model²⁸⁻²⁹. AVF creation before or after elastase infusion increases WSS, RWS and limits AAA progression (**Figure 2**). **Figure 3** demonstrates typical post-elastase AAA.

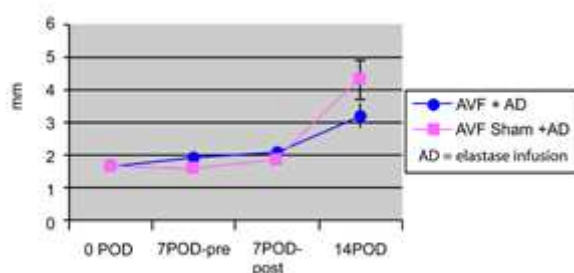


Figure 2. Femoral AVF or sham created 7 days prior to aortic elastase infusion (0 POD). Ordinate represents aortic diameter in mm. 7POD-pre and post diameters obtained during elastase infusion procedure. At final measurement (14 POD), AVF limits AAA diameter vs. AVF sham ($p < 0.01$). Reversing the order of procedures (infusion prior to AVF) produces similar results (data not shown).

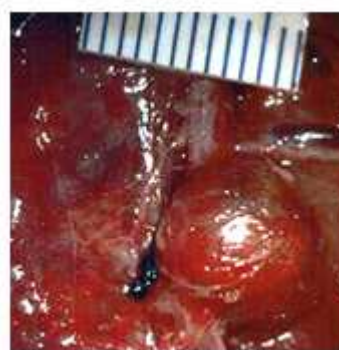


Figure 3. Infrarenal rodent AAA. Ruler demarcation in mm.

Unilateral common iliac artery ligation decreases rodent aortic wall shear stress in proportion to diminished aortic flow, again without affecting pressure (**Table II**). Seven days later, ligation produces larger AAA than elastase infusion alone (**Figures 4 and 5**).

Measurement	Baseline condition	Following iliac ligation
Flow (ml/mm)	19.7 ± 2.9	13.0 ± 3.9*

WSS (dynes/cm ²)	21.6± 4.6	14.2± 4.8*
Pressure (s/d (mean) torr)	168/126 (140)	168/127 (141)

* = p<0.05 vs. baseline conditions

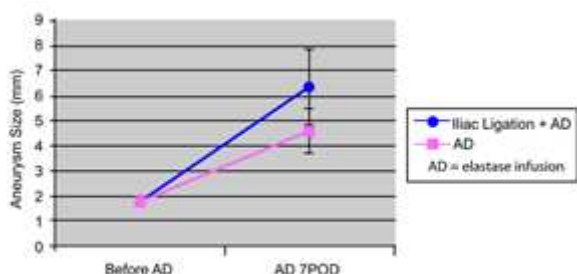


Figure 4: Aortic diameter prior to elastase infusion (Before AD) and 7 days following elastase infusion (AD 7POD), with and without unilateral common iliac ligation. Ligation augments AAA diameter (p<0.01).

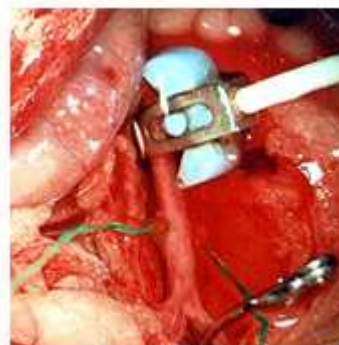


Figure 5: Rodent aortic prep immediately prior to elastase infusion. Note flow probe (white clip), sono crystals (green wires), and left iliac ligation clip (stainless)

Data obtained from these rodent models, as well as computational human aortic models³⁰ and MR-derived in-vivo human aortic flow data³¹ support the contention that increased AAA risk in amputees or paraplegic patients may well be due to diminished or asymmetric infrarenal aortic blood flow and associated low antegrade or oscillatory shear conditions in the infrarenal aorta. The rodent data also suggests that elevated antegrade shear stress present during sustained high flow conditions (following AVF creation in these experiments, or increased lower extremity activity in human subjects) may limit aneurysmal progression. The mechanisms responsible for modulation of AAA progression via hemodynamic influences are the current focus of our laboratory investigations.

The possibility that hemodynamic conditions may modify the natural history of AAA disease has broad public health implications for both chronically disabled patients as well as ambulatory but relatively sedentary individuals. In addition to myriad broad health benefits, a program of regular lower extremity exercise may prove useful in reducing aneurysm risk or rate of progression in AAA patients.

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