AAA Disease

Mechanism, Stratification, and Treatment

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ABSTRACT: Abdominal aortic aneurysm (AAA) is a common and frequently lethal disease of older Americans. No medical therapy has been proven effective in retarding progression of small AAAs prior to surgical repair. With the emerging ability of magnetic resonance (MR) flow imaging and MR-based computational analysis to define aortic hemodynamic conditions, and bio-imaging strategies to monitor aortic inflammation real time *in vivo*, the opportunity now exists to confirm the potential value of medical interventions such as supervised exercise training as first line therapy for small AAA disease.

KEYWORDS: abdominal aortic aneurysm; exercise; hemodynamics

INTRODUCTION

Advanced age, a history of cigarette smoking, male gender, and family history have traditionally been recognized as significant risk factors for abdominal aortic aneurysm (AAA) disease. Of these, smoking is the most significant; after adjustment for confounding risks, smoking is associated with a fivefold increase in AAA risk in men.[1] The incidence of unsuspected, asymptomatic AAA in men and women over 60 years of age is 4% to 8% and 0.5% to 1.5%, respectively.[1–7] Risks of rupture and sudden death are most closely related to diameter. AAAs $\geq$ 6 cm have a 10% to 20% chance of rupture within 12 months.[8–10] One-third of all AAAs eventually rupture if left untreated.

While more is being learned about AAA biology and behavior,[11] aneurysm diameter remains the most important clinical determinant for risk of rupture.[12] Typically identified as an incidental finding on abdominal imaging studies,

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the mean growth rate of small AAAs ($\leq$ 5.5 cm) is 2.6 mm/y, increasing with aneurysm diameter.[13,14] Surgical repair is currently the only effective method of AAA treatment. Despite numerous advances in surgical techniques and perioperative management, operative mortality for open elective and ruptured AAA repair has remained stable at 5.6% and 45.7%, respectively, for more than 20 years.[15] Postoperative survival has also not improved over the past two decades, perhaps due to more aggressive indications for repair offsetting improvements in surgical, medical, and anesthetic perioperative management. While newer endovascular exclusion strategies and devices limit the operative morbidity associated with open surgical repair in patients with suitable anatomy, these "endografts" have their own limitations, namely late migration, endoleak formation, and continued aneurysm expansion that mandate continued surveillance and frequent reintervention following initial technical success.[8]

The United States Preventative Services Task Force (USPSTF) recently updated its recommendations regarding the potential utility of screening ultrasound examinations to detect AAA disease. In 1996 the USPSTF had found insufficient evidence to recommend for or against routine AAA screening of asymptomatic adults. On the basis of a systematic re-review of updated information, including the results from four population-based, randomized, controlled screening trials, the Task Force recently concluded that AAA screening may reduce AAA-related mortality by 43% in men aged 65 to 75 years. Although surgical repair, as the only effective treatment, is associated with significant risks, the natural history of the disease outweighs these risks for men with AAAs greater than 5.5 cm. The potential utility of intervention for smaller AAA was also considered, but the risks of surgical repair greatly outweighed the potential benefit of reduced AAA rupture, even taking into account the likelihood that widespread screening will identify tens of thousands of new patients with smaller AAAs.[16]

The high prevalence and lethality of AAA disease stimulated the NIH-HLBI to issue a disease-specific request for applications (RFA) in December 1998. This RFA succeeded in generating considerable new knowledge regarding aneurysm pathogenesis and increased public awareness about AAAs. Despite these accomplishments, however, no potential therapeutic strategy has been demonstrated to improve clinical outcome in "worried well" patients with small, preclinical AAAs. Reducing the expansion rate of small AAAs by 50% would effectively eliminate the need for surgery in many older patients.[8] Strategies that have proven effective in limiting rodent AAA progression in biologically relevant models[17] have included matrix metalloproteinase (MMP) inhibition (doxycycline[18] and hydroxamic acids[19]), reduction of mural inflammation (angiotensin-converting enzyme (ACE) inhibitors,[20] suppression of NF-κB expression,[21,22] statins,[23,24] antioxidants,[25] osteopontin inhibition[26]) as well as hemodynamic conditioning[25,27,28] and medial smooth muscle cell augmentation.[29] Despite these promising results, there has been only one adequately

powered, randomized, clinical trial of medical therapy (propranolol) for small AAA disease. Beta-blockade was found to have no effect on the expansion rate of small AAA.[30] An additional trial testing doxycycline is ongoing.[31]

A major translational hurdle is the lack of direct indicators of aneurysm inflammation or inflammatory tone in models as well as patients. External aneurysm diameter, while of demonstrated value in predicting aneurysm rupture and patient survival in natural history studies, is less useful as the sole end point for validation or optimization of medical intervention strategies. This is true because expansion rate as the final common denominator of the degenerative process is likely to be relatively insensitive to more subtle but significant changes in AAA cellularity and pro- and anti-inflammatory mediator expression. Recently described analytical methods to estimate aortic wall strain from cross-sectional image data sets improve prediction of impending symptomatic evolution or rupture of large AAA but offer little additional insight regarding monitoring of less advanced disease. Circulating MMP-9 and hsCRP levels, while correlated with AAA status (present or absent, likelihood of clinical events, etc.) are not likely to be sufficiently disease specific to guide therapy for small aneurysm management; for example, reductions may not correlate with reduced AAA progression. We and others are currently working to identify and validate methods of directly assessing mural cellularity and inflammation *in vivo* to facilitate translation of promising therapies such as those described in the previous paragraph from bench to bedside.

Aneurysms occur with greatest frequency in the distal aorta. Although many theories have been advanced to explain this tendency, differential hemodynamic influences present along the length of the thoracic and abdominal aortas are potentially the most significant. Compared with the suprarenal aorta, the infrarenal environment in resting subjects is characterized by increased peripheral resistance, increased oscillatory wall shear stress (WSS), and reduced flow. These "resistive" hemodynamic conditions predispose arteries to degenerative diseases.[32] Infrarenal aortic MMP-9 expression is significantly greater than that present in the thoracic aorta during resting conditions. Transposition of the abdominal aorta to the thoracic position, however, reduces mural protease expression while reciprocal transposition of the thoracic aorta to the abdominal position increases levels to those seen in the infrarenal aorta *in situ.*[33] Major limb amputation,[34] chronic spinal cord injury,[35] and severe peripheral vascular disease[36] have recently been recognized as potential new risk factors for AAA disease, associations that highlight the pathogenic significance of resistive hemodynamic conditions. We have accumulated evidence over the last several years demonstrating that these high-risk sedentary hemodynamic conditions are completely obliterated with moderate levels of exercise.

In addition to directly modulating mural MMP-9 expression, luminal hemodynamic conditions may also significantly influence underlying aortic inflammatory tone.[37] Resistive aortic hemodynamics such as those found in the infrarenal aorta under sedentary conditions promote aortic inflammation and

the production of reactive oxygen species (ROS).[38,39] ROS in turn promote the upregulation and activation of proteolytic MMPs implicated in human AAA pathogenesis,[40–42] inactivate endogenous antiproteases, increase expression of proinflammatory transcription factors, chemokines and cytokines, and stimulate apoptosis.[43] The antioxidative[44] and antiapoptotic[45] influences of increased antegrade flow as is present in the aorta following lower extremity exercise may reduce aortic inflammation, maintain or improve intimal and medial vascular cell populations, and ultimately attenuate AAA progression.[25,46–51]

Aortic hemodynamic conditions directly reflect daily and lifelong patterns of lower extremity activity and exercise.[52–54] Despite considerable indirect evidence that aortic hemodynamic conditions influence AAA risk, the association between physical activity levels and disease progression has not been tested in a scientifically rigorous fashion. Coupled with the lack of effective treatment options for patients diagnosed with small AAAs, the significant disease-related anxiety present in patients who understand they have a life-threatening illness that carries a small chance of sudden death in the months or years prior to eligibility for surgical repair,[16,55] and the well-demonstrated benefits of exercise capacity for predicting cardiovascular and all-cause mortality,[56] confirming the relationship between activity level and disease risk may guide development of innovative new therapies while substantially improving the health of small AAA patients.

To confirm the degree to which aortic hemodynamic conditions influence human AAA disease progression, we recently conducted a prevalence survey in the "ultimate" sedentary patient population, spinal cord injury (SCI) patients. This population-based, controlled study included SCI patients $\geq$ 55 years old who had been injured and unable to walk for $\geq$ 5 years. Aortic and iliac artery diameters in SCI patients ($n = 123$) were compared to those of control patients ($n = 129$) without known abdominal or iliac aneurysms recruited from an age and risk–factor-matched ambulatory patient database prospectively maintained for the express purpose of examining SCI-related medical conditions. Aortic and iliac diameters were determined via transabdominal ultrasound. Normal aortic diameter (D) was defined as 2.0 cm (range 1.8–2.4); D $\leq$ 1.8 cm were "small," 2.5 $\geq$ D $\leq$ 3.0 "enlarged," and D $\geq$ 3.0 were defined as AAAs.[57] When grouped by 0.1 cm increments, aortic diameters in SCI patients trended higher than control, while iliac arteries were smaller. Overall there were significantly more AAAs, enlarged aortas, and small iliac arteries in SCI patients (all $P < 0.05$, TABLE 1). The prevalence of larger aortas in the SCI cohort was not explained by differences noted in traditional risk factors[58]

Diminished iliac artery diameter is expected in SCI patients as a result of the known propensity of arteries to remodel inward in response to sustained blood flow reductions. The paradoxical presence of increased aortic diameter and AAA prevalence in SCI patients is not consistent with known flow/remodeling relationships and supports the growing body of evidence that sedentary existence and chronically reduced/asymmetric aortic flow represent independent

TABLE 1. Aortic and iliac artery diameter in SCI and control subjects

Diameter	SCI (%)	Control (%)	*P*-value
Aorta (cm ± SD)	2.3 ± 0.9	2.0 ± 0.4	<0.01
≥3.0 cm (AAA)	11 (8.9)	4 (3.1)	0.04
≥2.5 cm (AAA + enlarged)	31 (25.2)	15 (11.6)	<0.01
Common iliac(s)	1.1 ± 0.3	1.1 ± 0.2	ns
≥1.5 cm (aneurysm)	9 (5.4)	12 (5.3)	ns
≥1.25 (aneurysm + enlarged)	26 (15.5)	44 (19.4)	ns
<1.0 cm (small)	80 (47.6)	59 (26.0)	<0.01

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risk factors for AAA disease.[34–36] Considered another way, normal aortic flow associated with ambulation reduces AAA disease risk in otherwise comparable patient groups. MR arteriography demonstrated increased aortic contours in SCI compared to control patients. The SCI patients were chosen at random for MR flow analysis from the larger SCI patient cohort after being demonstrated to have aortic diameters < 3 cm (did not meet AAA criteria) by ultrasound. Despite the absence of a formal aneurysm, we found a predilection for infrarenal aneurysmal degeneration despite diminutive iliac artery diameter present in the setting of spinal cord injury.

MR flow imaging and computational flow methods confirm the ability of lower extremity exercise to reduce proinflammatory hemodynamic conditions in the infrarenal aorta. In additional experiments we measured aortic flow in healthy subjects aged 20–30 and 50–70 years,[53,54,59] and atherosclerotic patients suffering from intermittent claudication (unpublished data) at rest and following lower extremity exercise. For these experiments we constructed a custom MR-compatible exercise cycle for the GE 0.5T open magnet.[60] Each subject was positioned such that his/her abdominal aorta was centered in the magnet. The cycle was then adjusted for subject size and strength. Cine phase-contrast MRI (PC-MRI) was performed to acquire time-resolved anatomic and through-plane velocity maps[61–63] perpendicular to the abdominal aorta at supraceliac and infrarenal levels at rest and during steady-state exercise conditions (150% of resting heart rate). The cine acquisitions were gated to the cardiac cycle using a plethysmograph, and images were reconstructed to 16 time points over the cardiac cycle.

We applied a level set segmentation method[64,65] to identify the flow lumen using cross-sectional aortic images for each time step. From these time-resolved segmentations and the associated velocity data we computed blood flow rate[63] and WSS.[66] Temporal oscillations of flow and shear were quantified by oscillatory flow (OFI)[60] and shear (OSI)[67] indices, respectively. In the older, healthy subjects, wall shear stress increased from 2.0 ± 0.7 to 7.3 ± 2.4 dynes/cm^2 in the supraceliac aorta and 1.4 ± 0.8 to 16.5 ± 5.1dynes/cm^2 at the infrarenal level (both $P < 0.001$) from rest to exercise. Blood velocity

surface plots for peak systole, end systole, and end diastole at the supraceliac and infrarenal levels at rest and during exercise for a healthy 20-year-old subject were constructed. These plots illustrated increased blood velocities at peak systole, end systole, and end diastole from rest to exercise for both the supraceliac and infrarenal locations. Moderate exercise increased infrarenal more than supraceliac flow, suggesting that lower extremity hyperemia occurs in part at the expense of mesenteric flow. Proinflammatory infrarenal aortic hemodynamic conditions present at rest (retrograde and oscillating diastolic flow) were obliterated during exercise. Aortic WSS increased during the entire cardiac cycle at all levels.

Although lower extremity exercise increases aortic flow and WSS, until recently little evidence was available to suggest that intermittent exercise produces sustained cardiovascular benefits. The exercise literature clearly demonstrates, however, that daily exercise periods are associated with marked reductions in all cause mortality and vascular-related complications in patients with cardiovascular disease.[68] Single episodes also produce sustained increases in human circulating progenitor cells,[69] redox-related gene expression, and when repeated over long intervals, conduit artery remodeling and disease resistance.[70] Similar shear-mediated effects present in our high-flow AAA models are associated with reduced aneurysm progression, albeit in a greatly truncated time frame due to continuously increased flow. It is likely, however, that gene expression and protein phosphorylation triggered by episodic increases in WSS modify arterial structure and function for sustained intervals following frequent intermittent exercise episodes.

We also developed and validated three-dimensional finite element methods for modeling blood flow[64,65,71–79] and applied these methods to computing flow in subject-specific models from CT and MRI data sets.[64,65,71,74,77–80] FIGURE 1 depicts velocity profiles computed for the abdominal aorta of a 19-year-old subject. The anatomic model was constructed from contrast-enhanced MR angiography data. Boundary conditions were specified on the basis of flow velocities measured at two discrete locations (supraceliac and immediately infrarenal aorta) at rest and during exercise using cine phase-contrast (PC)-MRI. The aorta demonstrates exceptionally complex flow patterns over the cardiac cycle under resting conditions, and the flow velocity field becomes more unidirectional and ordered under exercise conditions. While the blood flow in the abdominal aorta is still laminar (the solutions retain periodicity and do not exhibit random behavior associated with turbulent flow), it is clearly highly complex, particularly in the lower abdominal aorta in diastole.

Using updated finite element methods for solving nonlinear one-dimensional equations of blood flow that enforce pressure continuity and mass conservation at branch points as well as flow rate, pressure resistance, and impedance boundary conditions,[81–83] we modeled blood flow and pressure in the abdominal aorta of an SCI patient as well as an ambulatory control patient and AAA geometric model to analyze flow and WSS relationships in more

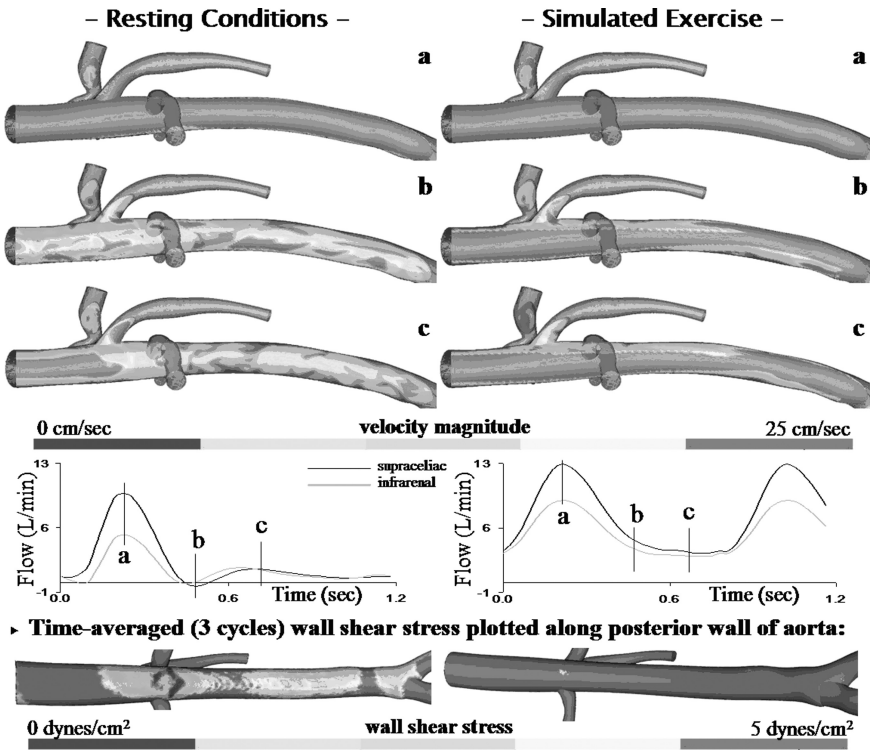

FIGURE 1. Subject-specific blood flow simulation in the abdominal aorta. The geometric model was constructed from MRA data and flow boundary conditions were based on PC-MRI data. (Adapted from B.T. Tang, C.P. Cheng, M.T. Draney, N.M. Wilson, P.S. Tsao, R.J. Herfkens, C.A. Taylor. Abdominal Aortic Hemodynamics in Young Healthy Adults at Rest and During Lower Limb Exercise: Quantification Using Image-based Computer Modeling. To appear in *American Journal of Physiology–Heart and Circulatory Physiology*.)

detail (FIG. 2). Models were constructed on the basis of MRA anatomic data. A fractal tree bifurcation model was generated for SCI vascular beds.[84] Starting with the common iliac arteries, this continued (using known diameter relationships) to the diameter of precapillary arterioles (10 μm). For the SCI patient with smaller common iliac arteries the peripheral resistance was increased. If the infrarenal flow was similar between SCI and ambulatory patients, this would be expected to result in higher pulse pressures in SCI patients, but this proved not to be the case. This can be explained by the long wavelengths (meters) of pressure wave travel in the arterial system. We did note a slower decay of the pressure pulse in SCI patients as compared to the normal subjects in our models. This can be understood by noting that the pressure decay time constant is related to the product of the proximal arterial compliance and the distal vascular resistance, the latter of which increases considerably in the SCI

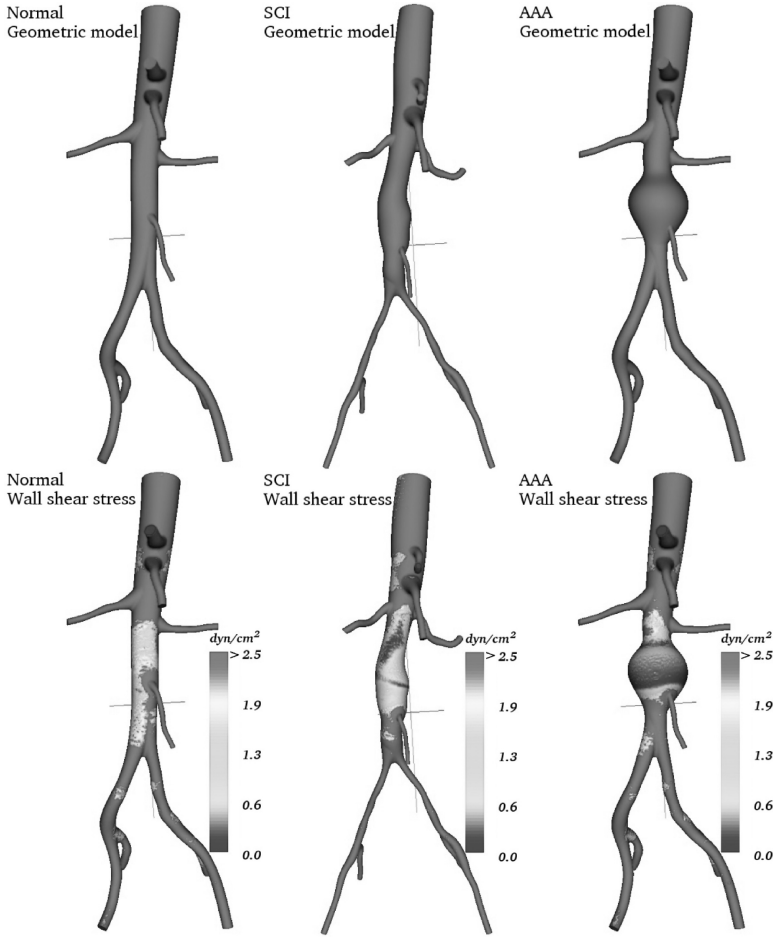

FIGURE 2. Three-dimensional aortic models (top) and resting WSS estimates at peak systole (below) of normal and SCI aorta and 4cm AAA, respectively.

patients. Furthermore, resting WSS differed significantly between conditions; roughly twofold lower in SCI and fivefold lower in AAA than in normal aorta. These data support our overall contention that SCI hemodynamic conditions accurately represent an extreme example of the consequences of sedentary existence and that proinflammatory hemodynamic conditions (e.g., reduced antegrade WSS) increase AAA risk in SCI patients. Beyond resting differences, however, SCI is unique in that no increase in aortic WSS occurs on the basis of ambulation. Considering that modest lower extremity exercise in older individuals increases resting aortic WSS approximately 16-fold, and that even sedentary, obese individuals walk on average 80 min/day or 2 km at

5 km/h in "displacement activities,"[85] even minimally active individuals generate at least 2× the total time-averaged WSS experienced by immobile SCI patients during a 24-h period. (1.3 h × 16 dynes/cm^2 + 22.7 h × 1dyne/cm^2 vs. 24 h × 1dyne/cm^2.) Therefore, we estimate at a minimum a fourfold time-averaged aortic WSS difference occurs between SCI and sedentary patients with even a minimum amount of activity. Pending investigations will confirm whether increasing activity levels confer similar levels of protection against AAA degeneration in ambulatory patients.

Higher levels of physical activity are associated with lower risks of death and cardiovascular disease morbidity. The long-term physiologic consequences of supervised exercise training include decreased resting heart rate, decreased heart rate, and systolic blood pressure at any matched submaximal workload, an increase in work capacity and maximal oxygen uptake as well as a faster return to resting hemodynamic conditions following cessation of activity. These responses may be due to peripheral or cardiac adaptations or both, but peripheral adaptations clearly become more significant with age. In 1984 Froelicher and Myers evaluated exercise conditions using maximal oxygen uptake treadmill and supine bicycle radionuclide testing.[86] Patients in the exercise group (72) underwent 1 year of supervised exercise sessions with exercise intensity progressing in standard fashion throughout the year. As compared to the control group, a significant training effect after 12 months was demonstrated by reduced resting and submaximal heart rates and increased measured and estimated maximal oxygen uptake. No changes were observed in maximal perceived exertion, respiratory exchange ratio, or systolic blood pressure between the two groups initially or at 1 year, or between the initial and 1-year tests within the exercise group. Analysis of variance confirmed that the training effect, including an increase in peak VO_2, occurred in subgroups of the exercise intervention patients relative to controls. However, no changes were noted in ECG or cardiac radionucleotide tests, suggesting that most of the beneficial changes associated with exercise occurred in the periphery.[86]

In addition to improving exercise capacity, exercise training significantly improves patient survival. In a meta-analysis of 48 scientifically valid, randomized trials including 8,940 patients undergoing cardiac rehabilitation compared to usual care, exercise training was associated with reduced all-cause mortality (odds ratio (OR = 0.80) and cardiac mortality (OR = 0.74). In addition, exercise training was associated with greater reductions in cholesterol, triglycerides, and systolic blood pressure.[87] Benefits of increased activity are also noted outside the supervised training scenarios: a meta-analysis of 30 cohort studies involving more than 2 million person-years of observation demonstrated a nearly linear decline in the risk of coronary heart disease with increasing levels of physical activity.[88] Both measured fitness level and self-reported physical activity confer protection. Of 6,213 men referred for exercise testing between 1987 and 2000, 842 also underwent assessment of self-reported adulthood activity patterns. The predictive power of exercise capacity and

activity patterns along with clinical and exercise test data were assessed for all-cause mortality during a mean of 5 years of follow-up. Considering clinical characteristics such as history of cardiovascular disease, smoking, hypertension, diabetes, obesity, and elevated cholesterol levels, exercise test data and self-reported activity patterns, expressing data by age-adjusted quartiles, exercise capacity HR (hazard ratio) per quartile = 0.72; 95% CI: 0.58 to 0.89, $P = 0.002$) and energy expenditure from self-reported activity during adulthood (HR per quartile = 0.72, 95% CI: 0.58 to 0.89, $P = 0.002$) were the only significant predictors of mortality. Age-adjusted mortality decreased per quartile increase in exercise capacity (HR for very low capacity = 1.0, HR for low = 0.59, HR for moderate = 0.46, HR for high = 0.28) and physical activity (HRs 1.0, 0.63, 0.42, and 0.38, respectively, $P < 0.001$). A 1,000-kcal/week increase in activity was approximately similar to a 1 metabolic equivalent (MET) increase in fitness; both conferred a mortality benefit of 20%.[89]

Although most such survival data have been obtained from cardiac rehabilitation studies, exercise capacity predicts mortality equally well in patients without coronary disease. Examining the same cohort of patients (as in Ref. 89), Drs. Myers and Froelicher classified their patients into two groups: 3,679 with an abnormal exercise test result or a history of cardiovascular disease or both, and 2,534 with a normal exercise test result and no history of cardiovascular disease.[56] After adjustment for age, the peak exercise capacity measured in METs was the strongest predictor of the risk of death among both normal subjects and those with cardiovascular disease. Absolute peak exercise capacity was a stronger predictor of the risk of death than the percentage of the age-predicted value achieved, and there was no interaction between the use or nonuse of beta blockers and the predictive power of exercise capacity. Each 1-MET increase in exercise capacity conferred a 12% improvement in survival,[56] and in a related study, health care costs were incrementally lower by an average of 5.4% per MET increase.[90]

Exercise training and increased levels of physical fitness are also highly effective in reducing systemic markers of inflammation relevant to AAAs. Serum high-sensitivity C-reactive protein (hsCRP) levels are increased in patients with AAA disease,[91] correlate in a stepwise fashion to increasing aneurysm diameter,[93] and apparently originate in part from within aneurysm tissue itself.[92] Exercise training reduces a wide range of serum inflammatory markers including hsCRP level: 2.5 h/week for 6 months reduced mononuclear production of atherogenic cytokines by 58% ($P < 0.001$), while production of atheroprotective cytokines rose by 36% ($P < 0.001$). Changes in cytokine production were proportionate to the time spent performing repetitive lower-body motion exercises ($P < 0.02$), suggesting a dose-response relationship. Serum hsCRP levels dropped by 35% with exercise training.[93]

Beyond the direct effects of training, self-reported physical activity shows a significant and inverse dose-response relationship with C-reactive protein and other serum indicators of inflammation, even after adjustment for the

confounding effects of traditional atherosclerotic risk factors. These effects are present in men with and without evidence of preexisting coronary disease.[94] Analyzing data from the > 13,000 participants ≥ 20 years old in the National Health and Nutrition examination survey (1988–1994) adjusted for age, sex, ethnicity, work status, education, cotinine concentration, hypertension, body mass index (BMI), waist-to-hip ratio, high-density lipoprotein cholesterol concentration, and aspirin use, the odds ratios for elevated C-reactive protein concentration were 0.98 (95% CI = 0.78–1.23), 0.85 (0.70–1.02), and 0.53 (0.40–0.71) for participants engaged in light, moderate, and vigorous physical activity, respectively, during the previous month compared to participants who did not engage in any leisure-time physical activity.[94] Similar results were obtained in an analysis of self-reported activity from 5,888 men and women ≥ 65 years of age in the Cardiovascular Health Study, although in that study multivariate regression analysis suggested that the association of higher levels of physical activity with lower hsCRP levels may be mediated by body mass index.[95] This is relevant in that the arterial wall is only one potential source of cytokines, which induce C-reactive protein production. Adipose cells also produce cytokines including IL-6, which induces hepatic CRP synthesis. Similar to the effects of exercise, caloric restriction and weight loss also lower IL-6 and CRP and may reduce overall systemic inflammatory tone.

This uncertainty regarding the mechanism by which exercise and activity level reduce inflammation (local aortic hemodynamic vs. metabolic response) highlights the critical need for the identification and validation of methods to directly quantify aortic inflammation or AAA-specific systemic disease markers. Even though CRP levels generally correlate with AAA size, elevated levels do not accurately identify subsets of small AAA patients who will ultimately demonstrate aneurysm enlargement.[92] This uncertainty is not limited to the role of CRP alone. Given the significance of inducible nitric oxide synthase (iNOS) activity and nitric oxide generation in human AAA pathogenesis,[96] and the potent efficacy of selective iNOS inhibition in limiting progression of experimental AAA at all stages of development,[97,98] the ability of exercise to reduce aortic iNOS and adhesion molecule expression and activity in hypercholesterolemic animal models[99] and TNF-α 1, IL-1, IL-6, and iNOS in lower extremity skeletal muscle (but not serum) of patients with congestive heart failure[100] suggests that direct aortic responses play a significant role in the ability of exercise training to reduce AAA progression.

SUMMARY

Despite intense public interest in AAA disease, the list of promising therapies as identified by experimental modeling is growing much more rapidly than is evidence supporting their efficacy in human disease. This “translational bottleneck” is accentuated by the lack of recognition of direct indicators

of aneurysm inflammation, inflammatory tone, and disease progression at the cellular level. The current standard for determination of AAA disease progression is external aneurysm diameter measurement.[93] This metric, while of demonstrated value in predicting aneurysm rupture or patient survival in natural history studies, is not well suited to the purpose of validating or optimizing medical intervention. Diameter enlargement is an indirect cumulative indicator of disease progression, relatively insensitive to more primary and fundamental changes in mural inflammation and remodeling. These fundamental molecular processes, the targets of experimental therapeutic strategies, are not quantifiable using current imaging or monitoring modalities.

Patients with reduced activity levels are at higher risk of AAA disease. Hyperemic luminal conditions present following exercise effectively reduce aortic inflammation, serum CRP levels, and progression of experimental AAAs. We are initiating a multicenter trial to compare exercise capacity and self-reported activity levels between patients with AAA of various sizes and to study the potential role of supervised exercise training to limit progression of small AAA disease. Our hypothesis, based on the exercise literature noted in the preceding paragraphs, is that increased activity reduces the incidence and progression of small AAA disease. These studies are also designed to identify novel bioimaging strategies to quantify and track aortic inflammation, providing new methods of monitoring disease progression and helping to eliminate the translational bottleneck that currently impedes progress in AAA research.

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