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Abdominal Aortic Hemodynamics in Intermittent Claudication Patients at Rest and During Dynamic Pedaling Exercise

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Abstract

Introduction—Lower extremity exercise has been shown to eliminate adverse hemodynamics conditions, such as low and oscillating blood flow and wall shear stress, in the abdominal aortas of healthy young and older adults.

Methods—We use cine phase-contrast magnetic resonance imaging and a custom MRI-compatible exercise cycle to quantify hemodynamic changes due to pedaling exercise in patients diagnosed with intermittent claudication.

Results and Conclusions—With only an average heart increase of $35 \pm 18\%$ and exercise workload of 36 ± 16 Watts, the patients experienced approximately 3- and 6-fold increases in blood flow, and 4- and 16-fold increases in wall shear stress at the supraceliac and infrarenal aortic locations, respectively. Also, all oscillations in flow and shear stress at rest were eliminated with exercise. Claudication patients experience 3 to 4-fold lower oscillations in flow and shear stress at rest as compared to healthy age-matched controls, likely due to reduced distal arterial compliance as a result of distal atherosclerosis. The magnitude of flow and shear oscillatory indices may be good indicators of distal arterial compliance and health, and may provide predictive power for the efficacy of focal interventions.

Keywords

Magnetic resonance imaging; exercise; blood flow rate; wall shear stress; intermittent claudication; atherosclerosis; hemodynamics

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1. Introduction

Atherosclerotic occlusive disease is much more prevalent and severe in the abdominal aorta versus the thoracic aorta [1]. This is hypothesized, in part, to be related to the adverse hemodynamic conditions present in the abdominal aorta, such as geometry, flow recirculation, high particle residence time, low wall shear stress, and oscillatory shear [2–5]. Furthermore, we know that these hemodynamic conditions in the abdominal aorta worsen with age due to the changing composition, geometry, and compliance of the vessel wall [6–10]. Exercise is known to improve these adverse conditions in healthy adults, with greater potential benefit in older adults due to worse basal conditions (lower mean wall shear stress and higher oscillatory shear) and greater increase in wall shear stress with similar exercise intensities as compared to young adults [9]. However, *in vivo* abdominal aortic hemodynamics in patients with intermittent claudication, and their changes due to dynamic lower limb exercise, has not been well documented, and comparative information would be useful for disease research and diagnostic purposes.

Lower extremity occlusive disease can cause intermittent claudication, rest pain, or even ulceration and gangrene by reducing blood flow to the lower extremities. Except for the most advanced stages of disease, ischemia only becomes evident during conditions of increased metabolic demand [11]. For this reason, some diagnostic exams involve approximating physiologic challenge that patients may experience during exercise. These techniques include inducing exercise stress by treadmill walking and pharmacologic stress realized either by vasodilation or increased heart rate. While the patients are in these stressed states, diagnoses are made based on reduced blood velocities measured by Doppler ultrasound, subnormal segmental arterial pressure ratios, and the presence of muscle pain. These same techniques are also applied to assess the efficacy of subsequent interventions.

Clinically, blood flow rate has been shown to be a strong predictor of patency following angioplasty, bypass, or arteriovenous fistula [12–14]. And for disease research, blood flow, among other hemodynamic conditions, is necessary to understand the mechanisms of atherosclerosis development. While Doppler ultrasound and ankle-brachial pressure measurements can be used to infer blood flow rate, they do not directly measure volume flow and are prone to inaccurate assessments. Some excellent magnetic resonance imaging methods have been developed to quantify blood perfusion into muscle during exercise, however, these methods do not quantify dynamic flow conditions in vessels [15]. Cine phase contrast magnetic resonance imaging (PC-MRI), however, can concurrently acquire temporally-resolved co-registered velocity and anatomic maps. This allows segmentation of large vessel lumens, and quantification of time-resolved volume flow rate and wall shear stress [16–17]. Combined with dynamic pedaling exercise, PC-MRI can provide information about the real-time impact of lower extremity exercise on abdominal aortic hemodynamics, and we hypothesize that there are quantifiable hemodynamically-protective effects. This information is also important for understanding hemodynamics in the context of improving diagnostic sensitivity.

In this study, we perform quantification of blood flow and wall shear stress in the abdominal aorta at rest and during upright cycling exercise in patients diagnosed with intermittent

claudication using an MR-compatible bicycle in an open MRI. We then compare this data with the hemodynamics of aged-matched healthy subjects.

2. Materials and Methods

2.1 Patient Recruitment and Imaging

The study protocol was approved by the Stanford University Panel on Human Subjects in Medical Research and the participants provided written informed consent. Six patients previously diagnosed with intermittent claudication were consented and included in this study. The patients were selected based upon conventional indications for iliac angioplasty and stenting, including: intermittent claudication rather than limb-threatening ischemia, focal stenosis rather than occlusion, and good runoff conditions [11]. Anthropometric data, heart rate, exercise workload, drop in ankle-brachial index (ABI) in the most affected leg following exercise, and hemodynamic conditions were recorded.

The study subjects were imaged in a 0.5 T interventional magnet (GE Signa SP, GE Medical Systems, Milwaukee, WI). Each subject was strapped to a seat in the interventional magnet with their abdomen in the center of the magnet bore and positioned such that they had full range of leg motion. A custom-built stationary exercise cycle was positioned and pedaling resistance was adjusted to accommodate for subject size and strength (Figure 1) [9]. Scans were performed during seated rest and steady state cycling exercise conditions, with the exercise condition defined as up to 150% of resting heart rate or as much as the patient could sustain during the scan. This exercise condition is within the range of light (35–59% of maximum heart rate) to moderate exercise (60–80% of maximum heart rate) [18]. Heart rate was displayed in real-time and subjects adjusted their pedaling speed to maintain a constant heart rate.

Cine PC-MRI techniques were used to obtain anatomic and through-plane velocity maps orthogonal to the aorta at the supraceliac and infrarenal levels at rest and during exercise. The following scan parameters were used: 25 ms TR, 9 ms TE, 30° flip angle, 10-mm slice thickness, 26×26 cm square field of view, 256×128 image matrix, and 150 cm/s through-plane velocity encoding gradient. The cine PC-MRI acquisitions were gated to the cardiac cycle using a plethysmograph placed on the right thumb, and data was retrospectively reconstructed to 16 time points within the cardiac cycle. Respiratory bellows were used to perform respiratory compensation [19].

2.2 Data Processing

We utilized level set segmentation to identify the aortic lumen from the MR magnitude data [20], and subsequently performed blood flow rate, wall shear stress, and lumen area calculations for each of the 16 time points within the cardiac cycle [9,16–17]. With these time varying quantities, temporal oscillations of blood flow and wall shear stress were computed as oscillatory flow index (OFI) [17] and oscillatory shear index (OSI) [21] as defined by the equations:

$$OFI = \frac{1}{2} \left(1 - \frac{\int_0^T Q dt}{\int_0^T |Q| dt} \right), \quad OSI = \frac{1}{2} \left(1 - \frac{\int_0^T \tau dt}{\int_0^T |\tau| dt} \right)$$

where Q is blood flow rate, τ is wall shear stress, and T is the period of the cardiac cycle. An oscillatory index of zero corresponds to positive flow rate or wall shear stress throughout the cardiac cycle whereas an oscillatory index of 0.5 corresponds to a mean flow rate or wall shear stress of zero over the cardiac cycle.

Paired t-tests were used to compare rest vs. exercise conditions and supraceliac vs. infrarenal locations. In addition, these patients were compared with aged-matched healthy subjects from a previous study [9] using unpaired t-tests. For multiple comparisons, the significance threshold ($P < 0.05$) was adjusted by Bonferroni-Holm correction [22]. All calculations were performed with the statistical package in Excel (Microsoft, Redmond, WA).

3. Results

3.1 Patient Information and Exercise Intensity

The six patients were all male, aged 62 ± 10 years, and all experienced claudication symptoms with pedaling exercise with a maximum ABI drop of 0.33 ± 0.16 (from 1.16 ± 0.25 to 0.83 ± 0.23) for the most affected leg. Only four of six patients were able to maintain pedaling the entire length of the scan, with only a single patient able to maintain a 50% increase in heart rate. The entire group had a heart rate increase of $35 \pm 18\%$ and average workload of 36 ± 16 Watts.

3.2 Hemodynamic Quantities for Claudication Patients

Hemodynamic quantities for rest and exercise are shown in Figure 2. From rest to exercise, aortic blood flow rate increased from 2.3 ± 0.5 to 4.5 ± 0.9 L/min ($P < 0.001$) at the supraceliac level and from 0.8 ± 0.2 to 3.3 ± 0.9 L/min ($P < 0.005$) at the infrarenal level. In addition, the supraceliac location experienced higher flow rate than the infrarenal location at both rest ($P < 0.001$) and exercise ($P < 0.01$). Similarly, from rest to exercise, wall shear stress increased from 2.5 ± 0.3 to 5.3 ± 1.3 dynes/cm² at the supraceliac level ($P < 0.005$) and from 2.0 ± 0.8 to 11.8 ± 1.9 dynes/cm² at the infrarenal level ($P < 0.001$). During exercise, the wall shear stress level at the infrarenal level exceeded that of the supraceliac level ($P < 0.005$). While there were no significant differences in oscillatory flow index between the supraceliac and infrarenal levels or between rest and exercise, oscillatory shear index was significantly higher at the infrarenal level as compared the supraceliac level at rest (0.09 ± 0.09 vs. 0.02 ± 0.03 , $P < 0.025$) and decreased at the infrarenal level from rest to exercise (0.09 ± 0.09 vs. 0.00 ± 0.00 , $P < 0.05$).

3.3 Comparison between Claudication Patients and Healthy Controls

Table I shows anthropometric and hemodynamic comparisons between the intermittent claudication patients of this study and healthy age-matched controls from a previous study [9]. There were no significant differences between the two populations for age, height, weight, and body mass index, however, the patients had significantly lower heart rate

increase due to exercise and lower average exercise workload as compared to the healthy controls. The claudication patients experienced significantly lower exercise supraceliac and infrarenal blood flow and wall shear stress as compared to the healthy controls. The patients also experienced significantly lower oscillatory flow index at the infrarenal level at rest, and lower oscillatory shear index at both the supraceliac and infrarenal levels at rest, as compared to the healthy controls. Finally, resting and exercise flow rate waveforms of the six patients were plotted against those of a representative control subject for visual comparison (Figure 3). The cardiac cycle time periods of the flow rate waveforms were normalized for easy comparison.

3.4 Hemodynamic Correlation with Exercise Intensity

Due to the highly varied exercise performance of the claudication patients, we investigated the relationship between heart rate increase and exercise workload to the changes in mean blood flow and wall shear stress. Table II presents the coefficients of correlation between the exercise-induced factor increases in mean flow rate and wall shear stress with percent heart rate increase and exercise workload. The coefficients of correlation (R) show that for the supraceliac location, factor increases in flow rate and wall shear stress correlate more strongly with percent heart rate increase (flow rate: $R=0.67$, wall shear stress: $R=0.73$) than exercise workload (flow rate: $R=0.023$, wall shear stress: $R=-0.26$). Whereas for the infrarenal location, factor increases in flow rate and wall shear stress correlate more strongly with exercise workload (flow rate: $R=0.68$, wall shear stress: $R=0.79$) than percent heart rate increase (flow rate: $R=0.22$, wall shear stress: $R=0.65$).

4. Discussion

4.1 Hemodynamic Changes with Exercise

The intermittent claudication patients of this study were not all able to sustain a 50% increase in heart rate during pedaling exercise as intended, and were not able to sustain a constant workload during the entirety of the scan. However, even with only $35\pm18\%$ increase in heart rate and significantly lower exercise workload as compared to the healthy controls, the patients still experienced 2.0 ± 0.5 and 4.4 ± 2.2 factor increases in supraceliac and infrarenal blood flow with exercise, respectively. Their increases in wall shear stress with exercise were even more dramatic, with 2.1 ± 0.3 and 6.7 ± 3.6 factor increases at the supraceliac and infrarenal levels, respectively. Furthermore, even with these light exercise conditions, oscillations in blood flow and wall shear stress were completely eliminated with exercise.

4.2 Comparison between Claudication Patients and Healthy Controls

While exercise workloads were lower for the claudication patients as compared to healthy controls, the hemodynamic changes due to exercise in the two populations shared some similarities. First, blood flow and wall shear stress increased significantly from rest to exercise, with greater changes at the infrarenal as compared to the supraceliac level. In response to exercise, visceral blood flow (difference between supraceliac and infrarenal blood flow) remained relatively constant, and thus all increased blood flow at the supraceliac level was directly transferred to the infrarenal level. This larger increase in flow,

as well as the significant tapering of the aorta (infrarenal lumen area/supraceliac lumen area = 0.57 ± 0.19), promotes higher wall shear stresses since the blood flow is forced to converge to a smaller cross-sectional area, thus transitioning a parabolic flow profile to a more plug-like profile [9]. In fact, this converging of flow and inferior increase in wall shear stress was very similar between the two populations, with the ratio of infrarenal to supraceliac wall shear stress nearly identical between patients and healthy controls at rest (Patients = 0.82 ± 0.32 , Controls = 0.80 ± 0.64) and during exercise (Patients = 2.16 ± 0.65 , Controls = 2.28 ± 0.62).

There were notable time-varying flow differences between the patient and healthy control populations. First, the claudication patients experienced lower peak-to-peak flow amplitudes, and significantly lower oscillatory flow index (approximately 4-fold lower) at the infrarenal level at rest as compared to healthy controls (Table I). This is likely a consequence of decreased distal arterial compliance and recoil in the claudication patients. In healthy people, the lower extremity arteries diametrically expand with the rush of blood during systole, and subsequently recoil at the beginning of diastole, pushing a portion of the blood superiorly towards the low flow resistance visceral arteries [9,17]. In our claudicant population, it appears that the peripheral arteries have dramatically muted expansion and recoil properties, which is characteristic of distal atherosclerosis [8,23]. This phenomenon is especially apparent in Figure 3, which shows the triphasic flow waveforms at the supraceliac and infrarenal levels of a representative healthy control at rest as compared to the constant flow rates during the entirety of diastole in the six claudication patients.

In addition, the oscillations in wall shear stress were also dramatically different between claudicants and healthy controls. The patients experienced significantly lower oscillatory shear index at the supraceliac (approximately 3.5-fold lower) and infrarenal (approximately 3-fold lower) levels at rest as compared to healthy controls (Table I). These are consequences of lower reverse flow and more biphasic flow waveform as compared to the controls. A biphasic waveform tends to have less contribution from higher frequencies, which translates to reduced peak-to-peak amplitude of wall shear stress as predicted by pulsatile flow theory [9,24]. Note that the claudicants do not express lower aortic lumen area compliance than the healthy controls (Table I), but in fact trend toward higher aortic lumen compliance at the infrarenal level. This means that shear oscillations do not get amplified in claudicants, and provides evidence that the arterial compliance loss in claudicants originates from the downstream arteries. In fact, it is likely that the stiffening of distal arteries promotes the compliance of the abdominal aorta due to increased pressure wave reflection [25].

4.3 Hemodynamic Correlation with Exercise Intensity

The stronger correlation of supraceliac blood flow with heart rate is consistent with the fact that heart rate intimately affects total cardiac output, which is more correlated to thoracic than abdominal aortic flow (Table II). The stronger correlation of infrarenal blood flow with exercise workload is consistent with the increased demand of blood flow to the lower extremities during cycling exercise. The relatively strong correlation of increased wall shear stress with exercise workload for the infrarenal aorta suggests that increased exercise

intensity may provide more hemodynamic benefit in the abdominal aortas of claudication patients.

4.4 Conclusions

Consistent with intermittent claudication, the patients experienced normal abdominal aortic blood flow at rest, but diminished flow during exercise since most of them could not achieve the exercise workloads realized by the healthy control subjects. With decreased capability to increase blood flow in the abdominal aorta during exercise, these types of patients may have faster rates of disease progression that accompany adverse hemodynamic conditions. Interestingly, decreased oscillations in flow and wall shear stress in the patients during rest conditions, arising from decreased compliance of diseased distal vessels, may somewhat counteract the low flow conditions in the infrarenal segment of the aorta. Because of the positive correlation of wall shear stress increase to exercise intensity, greater exercise intensity may provide increasing hemodynamic benefit in the abdominal aorta. Finally, the magnitude of flow and shear oscillatory indices may be good indicators of distal arterial compliance and health, and may provide predictive power for the efficacy of focal interventions. While this type of hemodynamic evaluation requires additional imaging and analysis, it could be performed prior to intervention to help predict efficacy, which could contribute to significant cost savings for the health care system.

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Figure 1.
Study subject pedaling a custom MR-compatible stationary exercise cycle in the GE 0.5T interventional MRI.

Figure 2.

Average mean blood flow rate (top left), oscillatory flow index (top right), mean wall shear stress (bottom left), and oscillatory shear index (bottom left) of six intermittent claudication patients at the supraceliac and infrarenal levels of the aorta at rest and during lower limb exercise. * indicates statistical difference between rest and exercise; ** indicates statistical difference between the supraceliac and infrarenal locations. Blood flow rate and wall shear stress increased significantly from rest to exercise for both anatomic locations with greater increases observed at the infrarenal location. Flow and shear stress oscillations present at rest were eliminated during exercise. At rest, the infrarenal location experienced lower mean flow and higher shear oscillations as compared to the supraceliac location.

Figure 3.

Aortic blood flow waveforms over the cardiac cycle for six patients with intermittent claudication (colored lines) and a representative healthy control subject (thick black line) at rest (left column) and exercise (right column) for the supraceliac (top row) and infrarenal (bottom row) locations. The cardiac cycle time periods were normalized for easy visual comparison. At rest, the claudication patients experienced relatively constant flow rate during diastole while the healthy subject exhibited lower flow at the beginning of diastole before increasing in later diastole. During exercise, the patients exhibited lower mean and peak-to-peak flow amplitudes.

Table I

Comparison of intermittent claudication patients with age-matched healthy controls

	Patients (N=6)	Controls (N=8)	P-Value
Age (years)	62 ± 10	57 ± 3	
Height (m)	1.74 ± 0.04	1.77 ± 0.06	
Weight (kg)	83.3 ± 11.2	76.6 ± 15.0	
BMI (kg/m²)	27.4 ± 2.5	24.3 ± 3.6	
Rest HR (bpm)	68 ± 11	63 ± 8	
Exercise HR (bpm)	92 ± 16	95 ± 12	
HR Increase (%)	35 ± 18	51 ± 3	0.028
Workload (Watts)	36 ± 16	59 ± 10	0.007
Max ABI Drop	0.33 ± 0.16	N/A	
Flow Rate (L/min)			
Rest-SC	2.3 ± 0.5	2.3 ± 0.4	
Exercise-SC	4.5 ± 0.9	6.0 ± 1.4	0.020
Rest-IR	0.8 ± 0.2	0.9 ± 0.3	
Exercise-IR	3.3 ± 0.9	4.9 ± 1.7	0.045
Wall Shear Stress (dynes/cm²)			
Rest-SC	2.5 ± 0.3	2.0 ± 0.7	
Exercise-SC	5.3 ± 1.3	7.3 ± 2.4	0.043
Rest-IR	2.0 ± 0.8	1.4 ± 0.8	
Exercise-IR	11.8 ± 1.9	16.5 ± 5.1	0.039
Oscillatory Flow Index			
Rest-SC	0.00 ± 0.00	0.00 ± 0.00	
Exercise-SC	0.00 ± 0.00	0.00 ± 0.00	
Rest-IR	0.03 ± 0.04	0.14 ± 0.09	0.026
Exercise-IR	0.00 ± 0.00	0.00 ± 0.00	
Oscillatory Shear Index			
Rest-SC	0.02 ± 0.03	0.07 ± 0.05	0.041
Exercise-SC	0.00 ± 0.00	0.00 ± 0.00	
Rest-IR	0.09 ± 0.09	0.25 ± 0.12	0.017
Exercise-IR	0.00 ± 0.00	0.00 ± 0.00	
Lumen Area (cm²)			
Rest-SC	3.6 ± 0.3	3.9 ± 0.7	
Rest-IR	2.0 ± 0.5	2.5 ± 0.5	
Lumen Area Compliance (%)			
Rest-SC	15 ± 10	16 ± 3	
Rest-IR	18 ± 11	10 ± 6	

Mean ± standard deviation of anthropometric, heart rate (HR), workload, ankle-brachial index (ABI), and hemodynamic data for six claudication patients and eight age-matched control subjects. Mean blood flow rate, mean wall shear stress, oscillatory flow index, and oscillatory shear index are presented for the supraceliac (SC) and infrarenal (IR) levels of the abdominal aorta at rest and during cycling exercise. P-values for quantities that are significantly different between the two populations are shown. The patients achieved significantly lower exercise intensity compared to the healthy controls, which corresponded with lower exercise flow and wall shear stress. The patients also experienced lower oscillatory flow at the infrarenal level at rest, as well as lower oscillatory shear at the supraceliac and infrarenal levels at rest.

Table II

Correlation of hemodynamic changes with exercise intensity in claudication patients

R – Coefficient of Correlation	$ R < 0.5$	Weak Corr.
	$0.5 < R < 0.8$	Moderate Corr.
	$ R > 0.8$	Strong Corr.
	Supraceliac	Infrarenal
<i>Factor Flow Increase vs.</i>		
Heart Rate Increase (%)	0.67	0.22
Exercise Workload (Watts)	0.23	0.68
<i>Factor WSS Increase vs.</i>		
Heart Rate Increase (%)	0.73	0.65
Exercise Workload (Watts)	-0.26	0.79

Coefficients of linear correlation for factor increases in mean flow rate and mean wall shear stress (WSS) from rest to exercise with percent increase in heart rate and exercise workload in intermittent claudication patients. For the supraceliac aorta, percent heart rate increase was a stronger correlator of flow rate and WSS increases, while for the infrarenal aorta, workload was a stronger correlator of flow rate and WSS increases.