Atherosclerosis, Endothelial Function, and Exercise in Coronary Artery Disease Patients

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The understanding of the development and progression of atherosclerosis has been greatly advanced in the past decade. In the 1970s, Ross proposed the response to injury hypothesis of atherosclerosis suggesting atherosclerosis begins with an injury to the arterial wall leading to endothelial denudation or “stripping of the endothelial lining of the artery”.1 Complementary to this hypothesis, recent evidence suggests that even the classic fatty streak, the earliest lesion common in infants and children, is an inflammatory lesion consisting of monocyte-derived macrophages and T-lymphocytes.2 This inflammation leads to endothelial dysfunction. Possible additional causes of endothelial dysfunction include:

- elevated low density lipoprotein cholesterol (LDL-C), particularly oxidized LDL-C;
- free radical induced damage caused by tobacco use, diabetes, and hypertension;
- genetic abnormalities;
- elevated plasma homocysteine;
- infectious agents such as chlamydia;
- obesity;
- sedentary lifestyle.

This article will address: 1. factors known to impair endothelial function and potential therapies, and 2. the effects of exercise training on endothelial function.

Case Study
A 50 year-old male presented to the Emergency Room (ER) with a recent 30-60 minute history of substernal chest pain radiating to the left shoulder and scapula precipitated by exertion. He rated the pain 3-4 on a 0-10 scale. He has had several of these episodes in the past 3-4 months, which usually resolved in a few minutes with rest. However, this episode was persistent. He denies nausea, dyspnea, or diaphoresis. He has become progressively more anxious about these episodes, which together with the persistence of this episode brought him to the ER. A resting ECG showed mild ST elevation with T-wave inversion in anterior leads. Troponin and CKMB band were mildly elevated suggesting a possible evolving myocardial infarction. He reported a history of untreated dyslipidemia, upper normal blood pressure of 134/88 mm Hg, and lack of regular physical exercise.
A lipid profile at the time of the presentation revealed a total cholesterol of 221 mg/dl (5.72 mmol/L), triglycerides of 211 mg/dl (2.38 mmol/L), HDL of 39 mg/dl (1.01 mmol/L), and LDL of 140 mg/dl (3.62 mmol/L). Homocysteine (8 mg/dl) and lipoprotein (a) [Lp(a)] (15 mg/dl) were within normal limits. High sensitive C-reactive protein (hsCRP) was slightly elevated at 2.8 mg/L. BMI was 28.2 with a waist circumference of 40.25 inches (102 cm). His father died of a myocardial infarction at age 58 years and his mother who is living had a TIA at age 72 years. His only sibling, a 48-year old brother, has a history of dyslipidemia, hypertension, and is overweight and physically inactive.

A cardiac catheterization was done within 90 minutes of the onset of chest pain which revealed an 85% proximal left anterior descending stenosis with irregularities distal to the lesion and two areas of 20-30% narrowing in the right and left circumflex coronary arteries. Left ventricular ejection fraction was 58%.

A percutaneous coronary angioplasty with implantation of a sirolimus eluting stent was performed across the LAD lesion. The patient tolerated this procedure without complications and was discharged after 48 hours of observation. Prior to discharge, a sestamibi exercise test was administered to 85% of maximal predicted HR. Results showed a 55% left ventricular ejection fraction and mild reversible perfusion abnormalities in the anterior and inferior walls. Medically, the patient was placed on Atenolol, 25 mg BID, Ramipril, 10 mg QD, 81 mg ASA QD, and Pravachol, 20 mg QD. He was advised to take daily a multivitamin with 400 mcg of folic acid and no iron, 200 IU’s of Vitamin E, 250 mg Vitamin C, and 100 mcg of Selenium. He was referred to Outpatient Cardiovascular Rehabilitation (CVR) to start within one week of discharge.

On entry into the CVR program, he underwent cardiopulmonary exercise testing and a prescription was written based on the anaerobic threshold and venous lactic acid accumulation. He was advised to consume an anti-atherogenic diet consisting of 20-25% fat, <7% saturated fat, <150 mgs/day cholesterol, 25-40 grams of fiber/day, and <2000 mgs/day sodium. He also was advised to consume more coldwater fish and foods rich in monounsaturated fats.

During the first exercise session, he experienced mild substernal chest pain rated 1 on a 0-4 pain scale, which was similar to his historical pain. The patient was hemodynamically stable and the pain resolved with rest. He was referred to cardiology and a repeat sestamibi exercise test was administered which was similar to the post discharge test. The patient was referred back to CVR and advised to exercise within tolerance for chest pain (not >1-1.5 on a 0-4 scale). He was advised to continue to aggressively manage risk factors for atherosclerotic progression.

This case illustrates a relatively common scenario in CVR programs. One explanation for the persistent, though less severe symptoms in light of an apparent successful revascularization procedure, is endothelial dysfunction. The patient has several risk factors for endothelial dysfunction including dyslipidemia, upper normal blood pressure, intermediate hsCRP level, positive family history, high fat diet, overweight, known CAD,
and sedentary lifestyle. Studies in patients with single vessel, occlusive disease demonstrate paradoxical coronary vasoconstriction in response to intracoronary injection of vasodilators such as acetylcholine in “visually” normal lumens.3

The Role of the Endothelium in Atherosclerosis
Traditionally, arteries have been thought of as simple, passive conduits through which blood flows. In the past 10-15 years, there has been a growing recognition that the endothelium plays a vital physiological role in vascular homeostasis. A dynamic balance between endothelial-derived vasodilating (nitric oxide or NO) and vasoconstricting (endothelin-1) substances has been shown to regulate vascular tone. In addition, it is recognized that the intact, functional endothelium contributes to preventing platelets and inflammatory cells from adhering to the vascular surface and forms an impermeable barrier to substances preventing them from entering the inner layers of the artery wall.

In persons without atherosclerosis, the predominant effect of endothelial activation and release of NO is vasodilation. Endothelial injury and denudation result in “dysfunction” (paradoxical vasoconstriction in response to known vasodilating agents), which appears to be the initiating event in the development of atherosclerosis. Endothelial dysfunction precedes the physical appearance of atherosclerosis on angiography.4

Clinical studies have documented that numerous risk factors for CAD cause endothelial dysfunction.5 Table 1 lists several risk factors associated with impaired endothelial-dependent vasodilation. The presence of these risk factors induces a number of detrimental changes in vascular biology including a decrease in NO bioavailability, increased oxygen radical formation, increased adhesion molecule formation (i.e. leukocytes, monocytes, soluble intracellular adhesion molecule-1), and increased endothelin-1 activity.6,7,8,9 These changes result in impaired vasodilatory capacity.

It is well established that endothelial damage and dysfunction is the initiating event in atherosclerosis. Recent studies have documented a high prevalence of atherosclerosis in asymptomatic teenagers and young adults, and endothelial dysfunction in obese children.10, 11 Endothelial dysfunction is also recognized as an important factor in acute coronary syndromes (ACS).12 Rozanski et al. recently compared finger blood flow responses to treadmill exercise in 57 patients with CAD and 50 apparently healthy volunteers.13 None of the healthy subjects manifested vasoconstriction throughout exercise whereas 53% of the patients with CAD demonstrated progressive vasoconstriction.

Although the basic and clinical research implicating endothelial dysfunction as the initiating event in atherogenesis is compelling, randomized clinical trials have not been completed which demonstrate reduced risk for coronary events in CAD patients following treatment to improve endothelial function. However a prospective study demonstrated that persons with endothelial dysfunction have a 3-4 fold increased risk of future coronary events independent of traditional risk factors.14 And a recent study of 503 persons without obstructive CAD reported that those persons with coronary endothelial dysfunction had a 4.32 fold greater risk of a cerebrovascular event than those
with out evidence of coronary endothelial dysfunction. Available evidence seems convincing and justifies instituting therapy to improve endothelial dysfunction.

Table 1: Risk Factors Documented to be Associated with Endothelial Dysfunction

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Associated Risk Factor</th>
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<tbody>
<tr>
<td>Dyslipidemia</td>
<td>Aging</td>
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<tr>
<td>Presence of oxidized LDL’s</td>
<td>Post-menopausal state</td>
</tr>
<tr>
<td>Presence of small, dense LDL’s</td>
<td>Insulin Resistance</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Impaired fasting glucose</td>
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<tr>
<td>Type 1 &amp; 2 diabetes mellitus</td>
<td>Acute post-prandial hypertriglyceridemia</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>Active and passive smoking</td>
</tr>
<tr>
<td>Elevated lipoprotein (a)</td>
<td>Psychosocial stress</td>
</tr>
<tr>
<td>Overweight</td>
<td>Physical Inactivity</td>
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</table>

Treatment of Endothelial Dysfunction

Numerous interventions have been shown to attenuate endothelial dysfunction in humans. Several studies have demonstrated improved endothelial function following lipid altering therapy. A recent study demonstrated improved endothelial function in type 2 Diabetes Mellitus patients with 3 days of cerivastatin therapy. Other studies have shown improved endothelial function following LDL pheresis and antioxidant therapy with Vitamin C. The data on Vitamin E is equivocal although a recent report found that 2 weeks of Vitamin E therapy decreased P-selectin in dyslipidemic patients suggesting an improved environment favoring vasodilation. Several reports have shown that interventions including ACE inhibitors, HMG-CoA reductase inhibitors, folic acid supplementation in hyperhomocysteinemic patients, and recently ACEII Receptor 1 blockers attenuate coronary endothelial dysfunction in patients with CAD. A variety of other interventions including aerobic exercise training have been shown to improve endothelial dysfunction (Table 2).

Chronic Physical Activity, Exercise Training, and Enhanced Endothelial Function

Two meta-analyses confirmed a 20-25% reduction in CVD mortality following participation in Cardiac Rehabilitation. Hammalainen et al. in a 10-year follow-up of cardiac rehabilitation following myocardial infarction, reported a 37% reduction in sudden death among patients participating in a multifactorial intervention program. Wannamathee et al. in a prospective 5 year cohort study, documented a 50% reduction in CVD mortality and morbidity in patients with documented CAD who became or remained active compared to those who remained sedentary. A recent 7-year follow-up investigation of post-CAD patients by Stiffen-Barry et al. reported similar results. Finally, the results of the ETICA study showed after 33 months of follow-up that 11.9% of 59 patients who exercise trained (26% increase in VO\text{\textsubscript{2}} peak) after PTCA and/or stent implantation had a recurrent event compared to 32.2% of 59 patients who did not exercise. Thus, it is established that exercise training in CAD patients improves survival. However, the mechanisms for this observed benefit are not completely clear.

Numerous studies have shown that regular exercise training in CAD patients improves lipids, diabetes, hypertension, obesity, and thrombogenic factors. However, the benefit
of exercise on mortality and morbidity in CAD patients is independent of the effect on risk factors. Exercise training also improves myocardial perfusion but has limited effect on the size and extent of atherosclerotic lesions. Recent studies suggest that a mechanism by which exercise training in CAD patients reduces progression of atherosclerosis and risk for recurrent events is improvement in vascular tone and endothelial function.

Haskell et al. used quantitative angiography to compare coronary vascular reactivity in ultra-distance runners and sedentary gender-age-matched men and women. There was no significant difference among groups in basal diameter of epicardial coronary arteries. However, during angiography, when sublingual nitroglycerin was injected, the coronary arteries of the ultra-distance runners showed a 200% greater increase in vasodilation than the sedentary group.

Hambrecht et al. investigated the effects of dynamic bicycle ergometer training for six months on endothelial function in congestive heart failure (CHF) patients. Twenty CHF patients were randomized to a control group (n=10) or an exercise training group (n=10). After training, peripheral blood flow increased significantly (p<0.05) in response to acetylcholine compared to no change in the control group. Peak oxygen uptake increased in the exercise group but not in the control group. Increase in peak oxygen uptake was correlated (r=0.64, p<0.005) with increases in endothelium-dependent changes in peripheral blood flow. Hambrecht et al. reported similar findings in another study of CHF patients (n=40) and the effect of exercise on endothelial function.

| Table 2: Interventions Demonstrated to Improve Endothelial Dysfunction |
|---------------------------------------------------------------|------------------|
| LDL lowering with pheresis                                   | Thermal therapy  |
| LDL lowering by statins                                      | Purple grape juice|
| LDL lowering by low fat diet                                 | Iron chelation    |
| ACE/ACE II receptor inhibitors                               | Black and green tea|
| L-Arginine                                                    | High monounsaturated diet|
| Moderate alcohol intake                                      | Smoking cessation  |
| Premenopausal status                                          | Anti-oxidant therapy|
| Exercise training                                            | Weight loss and loss of central body fat |

Exercise training has been shown to improve glycemic control in patients with diabetes mellitus and blood pressure in patients with Stages 1 & 2 hypertension. It is known that patients with diabetes or hypertension who exercise regularly and/or are physically fit have lower rates of CVD and all-cause mortality. The mechanisms facilitating these benefits of exercise are incompletely understood.

Higashi et al. studied forearm blood flow in 17 patients with Stage 1 hypertension. Ten patients were randomized to an exercise training group and seven to a control group. After 12 weeks of training, forearm blood flow response to acetylcholine infusion was
increased significantly (p<0.05) in the exercise training group compared to the control group. There also was an increase in acetylcholine-stimulated NO release. This study demonstrated improved endothelial-dependent vasodilatation following exercise training in Stage 1 hypertension patients mediated through increased endothelial release of NO. Recently a study of combined aerobic and resistance exercise for 8 weeks in patients with type 2 diabetes mellitus demonstrated enhanced endothelium-dependent vasodilatation in conduit and resistance vessels.

Cross-sectional studies have shown that age-related increases in arterial stiffness are attenuated in endurance-trained adults. Tanaka et al. in a longitudinal study of 20 middle-aged, sedentary men (mean age = 53 +/- 2 years), demonstrated that exercise training (walking/jogging, 40-45 minutes/session, 4-6 days/week at 70-75% of maximum heart rate) significantly improved arterial compliance. Arterial compliance was similar to middle-aged and older endurance-trained men. These effects were independent of changes in body mass, adiposity, blood pressure, or peak oxygen uptake. DeSouza et al. in a cross-sectional study of 68 sedentary or endurance-trained healthy male volunteers (age 22-35 and 50-76 years) found no age-related decline in forearm blood flow in response to acetylcholine in the endurance-trained men. In a sub-study of 13 middle-aged sedentary men who underwent a 12 week walking/jogging program (5-6 days/week, 40-45 minutes/session, at 70-75% of maximum heart rate), acetylcholine mediated forearm blood flow increased 30% (p<0.01) to levels similar to those found in young adults and middle-aged and older endurance-trained men.

In another cross-sectional study, Taddei et al. reported that endurance training can prevent the age-associated endothelial dysfunction through the restoration of NO availability consequent to the prevention of oxidative stress. These reports provide compelling evidence that endurance exercise training may prevent or attenuate the age-related decline in endothelium-dependent vasodilation and restore levels in previously sedentary middle-aged and older men.

A recent study by Hambrecht et al. demonstrated improved vasodilatory capacity in the coronary arteries of patients with documented CAD and endothelial dysfunction. Ten patients were randomized to an exercise training group and nine to a control group. Exercise training consisted of 4 weeks of 6 daily, supervised ten-minute sessions at 80% of peak heart rate. Paradoxical vasoconstriction of coronary arteries in response to acetylcholine infusion was reduced by 54% in the exercise group compared to the control group. Exercise training also resulted in significantly improved coronary blood-flow reserve (p<0.01) and flow-dependent coronary vasodilation (p<0.01) compared to no changes in the control group. This study was the first to demonstrate improved endothelial function following aerobic exercise training in the coronary arteries of patients with CAD and documented endothelial dysfunction.

Finally, Linke et al. recently investigated the systemic effects of lower body exercise training on radial artery endothelial function. Twenty-two male patients with
CHF (left ventricular ejection fractions = 24 +/- 2%) were randomized to either exercise training or an inactive control group. After 4 weeks, exercise trained patients showed a significant (p=0.001 vs. control group) increase in the baseline corrected internal diameter of the radial artery in response to acetylcholine infusion. In the training group, increases in agonist-mediated endothelium-dependent vasodilation correlated with changes in functional work capacity.

Summary
The growing knowledge that the luminal diameter of coronary epicardial and resistance vessels and major peripheral arteries are highly dynamic in response to flow-mediated (shear stress) and agonist-mediated (nitric oxide and endothelin-1) factors has greatly advanced the understanding of atherosclerosis. Ludmer et al. first observed a paradoxical vasoconstriction of atherosclerotic segments of coronary arteries in response to the infusion of acetylcholine. This paradoxical constriction was observed in angiographically “normal” arteries.

In addition, it has been observed that persons with major coronary risk factors often demonstrate endothelial dysfunction before anatomical atherosclerotic lesions can be observed on angiography. This has led to the concept that endothelial dysfunction is a key pathological feature in the early stages of atherosclerosis. Additionally, endothelial dysfunction also plays a significant role in ACS, by the relative inability of the vascular surface to inhibit platelet aggregation and also, perhaps, by contributing to plaque rupture as the initiating event in ACS. Recent clinical studies have consistently demonstrated that treatment and correction of major risk factors improves endothelial function. This has been observed for lipid, weight, blood pressure, and diabetes management and smoking cessation. Correction of impaired endothelial function also has been shown following treatment with statins, ace inhibitors, purple grape juice, folic acid, L-arginine, and other substances (Table 2).

Exercise training has recently been shown to improve endothelial function in patients with congestive heart failure, hypertension, diabetes mellitus, and CAD. Hambrecht et al. were the first to demonstrate that just four weeks of daily moderate intensity endurance exercise training in patients with CAD attenuated the paradoxical coronary vasoconstriction in response to acetylcholine. Linke et al. recently demonstrated in CHF patients that the enhanced endothelial function following exercise training is systemic in nature. These data provide compelling support for an important mechanism by which regular exercise may improve endothelial function and enhance coronary blood flow in patients with or at risk for CAD, and reduce the risk for atherosclerosis progression and recurrent events. Hambrecht et al recently reported that regular physical activity improves endothelial function in persons with CAD by increasing the phosphorylation of nitric oxide synthase.

Finally, at this time, the intensity, duration, and frequency of exercise to optimize enhancement of endothelial function are unclear. Goto et al recently compared the effects of mild (25% VO2 max), mild (50% VO2 max), and high (75% VO2 max) intensity exercise on endothelial function as assessed by forearm blood flow response to...
acetycholine (endothelial dependent) and isosobide dinitrate (endothelial independent). 53 Subjects were 26 healthy young men and they trained on bicycle ergometers, 30 minutes per session, 5-7 days per week for 12 weeks. The results suggested that only moderate intensity exercise improved endothelial dependent vasodilation while neither intensity enhanced endothelial independent vasodilation. More studies with larger sample sizes and which include women, middle-aged and older adults, and persons with CAD and CVD are necessary before definitive recommendations can be made. The few studies that have been completed would suggest that a common prescription of 30 to 45 minutes of moderate to vigorous intensity (50% to 70% of maximal oxygen uptake reserve or heart rate reserve), 4-5 days per week are effective, but that this exercise must be coupled with other daily activity, because the benefits of exercise on the endothelium may be acute and related to recent exercise.

References
12. Davies M.J. Going from immutable to mutable atherosclerotic plaques. Am J Cardiol 2001;88(suppl):2F-9F.


