Effects of resistance training on endothelial progenitor cells in young smokers: a pilot study

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EFFECTS OF RESISTANCE TRAINING ON ENDOTHELIAL PROGENITOR CELLS IN YOUNG SMOKERS: A PILOT STUDY

by

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DEDICATION

I would like to dedicate this work to my loving parents, for supporting all of my endeavors, no matter how foolish or asinine. I would also like to give special thank Dr. Theresa Davies for helping me through the writing submission process.
EFFECTS OF RESISTANCE TRAINING ON ENDOTHELIAL PROGENITOR CELLS IN YOUNG SMOKERS: A PILOT STUDY

ANDREW T. DAM

ABSTRACT

Background: Research has shown that cigarette smoking is linked to endothelial dysfunction, which represents a key early step in the development of atherosclerosis. This association between endothelial dysfunction and atherosclerosis also suggests that the status of an individual's endothelial function can be a potential indicator of a cardiovascular health. To better understand endothelial dysfunction, researchers have started to quantify peripheral circulating endothelial progenitor cells as effective biomarkers for cardiovascular risks. Many cardiovascular disease risk factors are immutable; however, recent studies have recognized resistance training as a viable strategy for cardiovascular disease prevention. Furthermore, there are only a few studies that focus on endothelial progenitor cells as a biomarker to investigate the effects of resistance training on cardiovascular health. This pilot study explored the effects of resistance intervention on circulating endothelial progenitor cells in both women and men smokers.

Methods: A group of 12 healthy young smokers were randomized into a 12-week RT or control group. Measurements were taken once at the beginning of
the study and once again at the end of the study (week 13). Participants were assessed for any changes from baseline in endothelial progenitor cell count, nicotine dependence and relative strength.

**Results:** Average endothelial progenitor cell count decreased in both RT and control from baseline. However, RT saw a larger decrease in CD34+, CD133+, and KDR when compared to control. We observed a decrease in the mean Fagerstrom Test for Nicotine Dependence score for RT, while control saw an increase from the average baseline score. We also noted an increase in average relative strength from RT participants, while relative strength slightly decreased in control. There were no significant changes in body weight or body mass index in both groups.

**Conclusion:** This is the first study to investigate the effects of RT on EPC count in young smokers. The findings from this study do not suggest a positive relationship between RT intervention and EPC count. Results did indicate that RT had a lower nicotine dependence compared with control following intervention, which provides more evidence for RT as an adjunctive strategy for smoke cessation. However, due to the low sample number in this study, an adequately powered experimental design is warranted.
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LIST OF ABBREVIATIONS

1-RM................................................................. One Repetition Maximum
ACS ............................................................... American Chemical Society
AT ................................................................. Ammonia Technology
BB ........................................................................ Barbell
BMI ......................................................................... Body Mass Index
CDC .......................................................... Center for Disease Control and Prevention
CHD ............................................................... Coronary Heart Disease
CNS ............................................................... Central Nervous System
CPD ................................................................. Cigarettes Smoked Per Day
CPD-II .............................................................. Cancer Prevention Study II
CPS-I ............................................................... Cancer Prevention Study I
CTRC .......................................................... Clinical and Translation Research Center
CVD ............................................................... Cardiovascular Disease
DAP ................................................................. Diammonium Phosphate
DB ................................................................. Dumbbell
EKG ................................................................. Electrocardiogram
eNOS .............................................................. Endothelial Nitric Oxide Synthase
EPC ............................................................... Endothelial Progenitor Cells
FMD ............................................................... Flow-Mediated Dilation
FMO ............................................................... Fluorescence Minus One Tube
FTND ............................................................. Fagerström Test for Nicotine Dependence
GVL .......................................................... Gamma-Valerolactone
HbA1c .......................................................... Glycated Hemoglobin A1c
HDL .......................................................... High-Density Lipoprotein
IPAQ .......................................................... International Physical Activity Questionnaire
KDR .......................................................... Kinase Insert Domain Receptor
LBM .......................................................... Lean Body Mass
LDL .......................................................... Low-Density Lipoprotein
MAP .......................................................... Monoammonium Phosphate
NFMD .......................................................... Normalized FMD
NH₃ .......................................................... Ammonia
NH₄OH .......................................................... Ammonia Hydroxide
NO .......................................................... Nitric Oxide
OGTT .......................................................... Oral Glucose Tolerance Test
PAH .......................................................... Polycyclic Aromatic Hydrocarbons
RM .......................................................... Repetition Maximum
ROS .......................................................... Reactive-Oxygen Species
RS .......................................................... Relative Strength
RT .......................................................... Resistance Training
UCLA ...................................................... University of California, Los Angeles
VEC .......................................................... Vascular Endothelial Cadherin
VWF .......................................................... Von Willebrand Factor
WHO .......................................................... World Health Organization
INTRODUCTION

Tobacco Use

A landmark report published in 1964 by the Surgeon General’s Advisory Committee on Smoking and Health established the link between smoking, lung cancer, and other lung diseases as well as possible correlation between smoking and other cardiovascular diseases\(^1\). The 1964 report had wide effects across the world and led to more public awareness of the adverse effects of cigarette smoking as well as greater efforts to change policies on advertising, warning labels, and restrictions on tobacco industries. Since publication of the report by the Surgeon General’s Advisory Committee on Smoking and Health in 1964, cigarette consumption has declined every year\(^1\). Public awareness on the consequences of cigarettes also shifted since the report, and the link between cigarettes and its harmful effects have well established itself in the domain of public knowledge. In spite of these great accomplishments, the tobacco epidemic is still one the greatest public health concerns ever encountered. It is estimated that there are currently over 1 billion smokers worldwide, or about 16% of the global population\(^2,3\). Moreover, cigarette smoking continues to be the leading cause of preventable deaths in the United States, causing about 443,000 premature deaths every year\(^4\). The World Health Organization (WHO) published a report on the global tobacco epidemic estimating the prevalence of smoking in different countries, as shown in Table 1\(^1\).
Table 1: Estimates of the prevalence of current cigarette smokers for selected countries of the World Health Organization, 2009. Estimates are standardized to age distribution and based on whether smoking at the time of survey was daily or non-daily. (Source modified from the U.S. Department of Health and Human Services)

<table>
<thead>
<tr>
<th>WHO region</th>
<th>Member states</th>
<th>Males (%)</th>
<th>Females (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>North America</td>
<td>United States</td>
<td>28</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Canada</td>
<td>19</td>
<td>16</td>
</tr>
<tr>
<td>Europe</td>
<td>Denmark</td>
<td>30</td>
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<tr>
<td></td>
<td>Finland</td>
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<td>22</td>
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<tr>
<td></td>
<td>France</td>
<td>36</td>
<td>27</td>
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<td></td>
<td>Germany</td>
<td>33</td>
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<td>Netherlands</td>
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<td></td>
<td>Switzerland</td>
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<tr>
<td></td>
<td>United Kingdom</td>
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<td>23</td>
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<tr>
<td>Western Pacific</td>
<td>Australia</td>
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<td>19</td>
</tr>
<tr>
<td></td>
<td>China</td>
<td>50</td>
<td>2</td>
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<tr>
<td></td>
<td>India</td>
<td>11</td>
<td>1</td>
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<td>Japan</td>
<td>42</td>
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<td></td>
<td>Republic of Korea</td>
<td>53</td>
<td>6</td>
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<tr>
<td></td>
<td>Philippines</td>
<td>47</td>
<td>10</td>
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</tbody>
</table>

The addictive nature of nicotine makes cessation attempts difficult for smokers, with only about 4% to 7% of people being able to successfully quit smoking at any given attempt without the use of medication. According to the Center for Disease Control and Prevention (CDC), there are over 7,000 chemicals and compounds in cigarette smoke. Of these compounds and chemicals, hundreds are toxic to humans and more than 70 have been identified as carcinogens. The carcinogens of most concern are polycyclic aromatic hydrocarbons (PAH), N-
nitrosamines, aromatic amines, 1,3-butadiene, benzene, aldehydes, and ethylene oxide because of carcinogenic potency and levels found in cigarette smoke\textsuperscript{8}. Furthermore, the tobacco industry has devoted a large amount of research and developments to the use of additives to cigarettes, and have acknowledged using 599 different cigarette additives\textsuperscript{9}. Although tobacco companies claim that these additives are used to reduce the harshness and improve the taste of cigarettes, one study has shown that over 100 of these additives can enhance the addictiveness of cigarettes, and mask symptoms and illnesses linked to smoking behavior\textsuperscript{10,11}. \textbf{Figure 1}\textsuperscript{11} shows a summary of the pharmacological and chemical effects of cigarette additives.
Smokers tend to have a much higher chance of developing cancers when compared to non-smokers. According to WHO, lung cancer is the most common form of cancer worldwide. It is estimated that smoking contributes to 80%-90% of all lung cancers, with over 150,000 Americans died from lung cancer alone in
2014\textsuperscript{13}. Compared to non-smokers, men and women who smoke are 23 times and 13 times more likely to develop lung cancer, respectively\textsuperscript{13}. Secondhand smoke also causes premature death and disease in those who do not smoke. For example, non-smokers who report being exposed to secondhand smoke at home or work increase their chance of developing lung cancer by 20\%-30\%\textsuperscript{9}. Although lung and cardiovascular diseases are commonly associated with smoking, there are some cancers not normally associated with smoking that are more likely in smokers such as stomach, pancreatic, and bladder cancer\textsuperscript{14}.

Many components of cigarette smoke, when metabolized or transformed, may lead to cancer, as show in Figure 2\textsuperscript{1}.
Figure 2: Overview of The Causation of Cancer by Carcinogens in Cigarette Smoke. Smoking causes cancer indirectly through cigarette smoke metabolites or products of transformation. The resulting DNA adducts react with nucleic acids and cause mutations in oncogenes or tumor suppressing genes that can lead to tumor growth. (Source from the U.S. Department of Health and Human Services³)
There are some constituents of cigarettes or their metabolites that bind to growth receptors, which may activate secondary messenger pathways that can lead to carcinogenesis\(^1\). Furthermore, cigarette smoke also contains carcinogens which, while do not cause cancer themselves, may enhance cigarettes carcinogenic effects\(^1\). Epidemiologic studies have also investigated whether the risk of lung cancer death in smokers has changed over time. In one study by The American Chemical Society (ACS), results from two prospective cohort studies conducted over 20 years apart were compared in order to assess the effects of changes in the composition and design of cigarettes on the American smoker. Their findings showed that the risk of lung cancer deaths increased dramatically in the second cohort after controlling for measured differences in the duration and amount of cigarettes smoked per day between the smokers in the two studies\(^1\). Interestingly, the rate of lung cancer mortality remained unchanged for never smokers in this study, suggesting that the increased risk observed in smokers were unlikely to have occurred due to other risk factors for lung cancer in the general population\(^1\). The results from these studies have suggested that the changes in composition and design of cigarettes since the 1950s are responsible for the increased risk of lung cancer mortality\(^1\). **Figure 3**\(^1\) shows the analysis of the two studies for men and women smokers and never smokers.
Figure 3: Death Rates from all Lung Cancers, Cancer Prevention Study I (CPS-1) and Cancer Prevention Study II (CPS-II), 1959-1965 and 1982-1988. All data was adjusted for age, duration of smoking, and number of cigarettes smoked per day. Women smokers saw a larger increase in rate compared to male smokers by the end of the Cancer Prevention Study II. Each data point represents the death rate measured at the end of the six year interval for both studies. (Source modified from Thun, et al., 1997)

Cardiovascular Disease

Cigarette smoking and exposure of nonsmokers to tobacco smoke is known to increase the chances of developing cardiovascular disease (CVD). CVDs are the leading cause of death worldwide, causing over seven million deaths in 2008, or about 13% of total global mortality. Table 2 lists the prevalence of CVDs in the United States in 2008. The term “cardiovascular disease” usually refers to conditions affecting the heart that can lead to myocardial infarction, or heart attack. These include, but are not limited to, hypertension, atherosclerosis, coronary heart disease, congenital heart defects, and arrhythmias.
Table 2: Prevalence of Cardiovascular Diseases in the United States, 2008. AMI= acute myocardial infarction; CHD= coronary heart disease. (Source modified from The National Heart, Lung, and Blood Institute, 2012^{17})

<table>
<thead>
<tr>
<th>Disease</th>
<th>Prevalence</th>
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</thead>
<tbody>
<tr>
<td>CVD</td>
<td>82,600,000</td>
</tr>
<tr>
<td>Hypertension</td>
<td>76,400,000</td>
</tr>
<tr>
<td>CHD</td>
<td>16,300,000</td>
</tr>
<tr>
<td>AMI</td>
<td>7,900,000</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>9,000,000</td>
</tr>
<tr>
<td>Stroke</td>
<td>7,000,000</td>
</tr>
<tr>
<td>Heart failure</td>
<td>5,700,000</td>
</tr>
<tr>
<td>Congenital heart defects</td>
<td>1,000,000</td>
</tr>
<tr>
<td>Arterial fibrillation</td>
<td>2,200,000</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>8,500,000</td>
</tr>
</tbody>
</table>

The single most important risk factor for developing CVDs is age, which poses as a big public health concern in the near future as the mean age of the population continues to increase in industrialized countries through unprecedented advances in disease prevention, diagnostics, and treatment^{18}. Some factors for CVD are immutable: age, gender, and family history^{1}. In spite of this, CVD is common among both genders and all ethnic/racial groups^{1}. The age-adjusted annual death rates for CVD have continued to remain higher for men, and are highest among non-Hispanic Blacks across all age groups^{1}. **Figures 4^{17}** and **5^{17}** depict the death rates for heart diseases in men and women, respectively, by age and race/ethnicity. Although some risk factors are unchangeable, many
important are modifiable through lifestyle changes, e.g., limiting tobacco use, exercise, healthy eating, and avoiding excessive alcohol consumption.

Figure 4: Death Rates Caused by Heart Diseases in Men by Age and Race/Ethnicity. *Non-Hispanic. (Source modified from The National Heart, Lung, and Blood Institute, 2012*)
Figure 5: Death Rates Caused by Heart Diseases in Women by Age and Race/Ethnicity. 
*aNon-Hispanic. (Source modified from The National Heart, Lung, and Blood Institute, 2012)\(^7\)

Research has shown that the top two leading preventable causes of death in the United States can be linked to tobacco use and obesity\(^9\). According to a report published by the U.S. Department of Health and Human Resources, two thirds of CVD deaths are attributed smoking in both men and women\(^1\). Although the absolute rate of CVD is higher in men than women, the increments in risk from smoking yields larger relative risks for women compared to men, suggesting that a high proportion of CVD in women are attributed to smoking (the female/male ratio being 1.25)\(^1\). Moreover, the amount of cigarettes smoked per day is an
important factor for determining relative risk (RR) of mortality, with a positive correlation shown between amount of cigarettes smoked per day and RR\textsuperscript{1}.

**Smoking and Endothelial Function**

The cells that line blood vessels make up the vascular endothelium. The endothelium is central for normal cardiovascular function, by promoting blood vessel dilation, thrombosis, and exerting anti-inflammatory effects\textsuperscript{1}. When endothelial function is impaired, the activation of chemical signals within the endothelium is compromised and is characterized by a proinflammatory, procoagulatory, and proproliferative disease state\textsuperscript{20}. **Figure 6**\textsuperscript{20} is an overview of the various factors affecting the endothelium and the consequences of its dysfunction.
Figure 6: Mechanism of Endothelial Dysfunction and the Resulting Consequences. Cigarette smoke falls under traditional risk factors and is a major contributor to endothelial dysfunction. Vascular damage will lead to atherosclerosis and eventually cardiovascular disease, the number one cause of mortality worldwide (Modified from Hadi et al., 2005).

One important mechanism by which the vascular endothelium operates is through the production of nitric oxide (NO). NO is a potent inhibitor of both leukocyte and platelet aggregation and adhesion. This offers protection from fibrous plaque formation as well as white cell adherence, events that are characteristic of atherosclerosis.
Cigarette smoke and its constituents form free radicals and reactive-oxygen species (ROS), which reduced the availability of NO and promotes endothelial dysfunction. Endothelial nitric oxide synthase (eNOS) is responsible for much of the NO production in the vasculature. Interestingly, eNOS expression has been shown to increase rather than decrease in response to cardiovascular risk factors. The increase in eNOS is likely due to the increased presence of ROS, which enhances eNOS expression through transcriptional and posttranscriptional mechanisms. In spite of this increased expression, ROS react with the NO produced by eNOS and converts the functional NO into another ROS, causing further oxidative stress on the vasculature. Figure 7 depicts the possible mechanism through which cardiovascular risk factors cause endothelial dysfunction.
**Figure 7: Mechanism by Which Cardiovascular Risk Factors Lead to Endothelial Dysfunction.** NADPH oxidase is upregulated in parallel with eNOS in response to cardiovascular risk factors. Their respective products form to create ONOO$^-$, causing oxidative damage to eNOS and producing more ROS. (Source modified from Forstermann et al., 2006$^{21}$)

**Endothelial Progenitor Cell Overview**

Endothelial cells make up the monolayer of cells lining the vascular endothelium. Following an acute stress injury of the vascular endothelium, the endothelial cells are destroyed by programmed cell death. At this point, regeneration of the endothelium is important to mitigate atherosclerotic plaque development$^{23}$. Because endothelial cells are terminally differentiated, another type of cell is needed for endothelial repair. Many studies have shown that endothelial
progenitor cells (EPCs) fulfill this role\textsuperscript{23}. Figure 8\textsuperscript{23} shows a depiction of how EPCs respond to damaged endothelium. Endothelial progenitor cells are a rare subset of circulating, bone marrow-derived cells that are involved in postnatal neovascularization and neoendothelialization following endothelial injury\textsuperscript{24}. EPCs have the potential to proliferate and to differentiate into endothelial cells, however, there is still debate as to how the damaged endothelial cells communicate with EPCs to initiate repair\textsuperscript{23}. Lower counts of EPCs are associated with cardiovascular risk factors and vascular dysfunction, and experiments have shown that diminished EPC counts are linked to impaired regenerative potential\textsuperscript{25}. Table 3\textsuperscript{24} shows various factors that influence the number of circulating EPCs.
Figure 8: Mobilization and Repair of Damaged Endothelium. Circulating EPCs home in on the site of vascular injury through an unknown intracellular signaling pathway. Once at the endothelium monolayer, EPCs may differentiate into mature endothelial cells or transdifferentiate into vascular smooth muscle cells. (Source from Hristov et al., 2003).

Table 3: The Pathological and Physiological Factors that Have Been Found to Affect the Number of EPCs in Systemic Circulation. Patients with risk factors for ischemic cardiovascular disease have shown to have a rapid increase in circulating EPCs. In contrast, those suffering from limb ischemia and acute myocardial infarction show a rapid increase in circulating EPCs Modified from Hristov et al., 2003)

<table>
<thead>
<tr>
<th>Conditions or Factors</th>
<th>Changes in Number of EPCs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular risk factors</td>
<td>Decreased</td>
</tr>
<tr>
<td>Limb Ischemia</td>
<td>Increased</td>
</tr>
<tr>
<td>Acute myocardial Infarction</td>
<td>Increased</td>
</tr>
<tr>
<td>Vascular Trauma</td>
<td>Increased</td>
</tr>
</tbody>
</table>
Endothelial Progenitor Cell Characterization

In general, EPCs are characterized by the expression of three biomarkers: CD133⁺, CD34⁺, and vascular endothelial growth factor receptor-2 [also termed receptor, or (KDR)]²⁶. Cells that display a mix of CD133⁺/CD34⁺/KDR, but do not express vascular endothelial cadherin (VEC) and von Willebrand factor (vWF) are typically localized in the bone marrow and not the peripheral circulation²³. VEC is expressed in mature EPCs and endothelial cells (EC), and play a role in the cohesion and organization of intercellular junctions within the endothelium²⁷. VEC is also necessary for proper vascular development by maintaining newly formed vessels²⁸. vWF plays an important role in blood coagulation and is expressed in mature EC and EPCs. The more mature EPCs found circulating in the peripheral circulation will be show a positive expression for CD34⁺ and KDR, but will have lost the expression of CD133²³. Once EPCs begin to differentiate into more mature ECs, they begin to show a high expression of KDR, VEC, and vWF, but no expression of CD133²³. Therefore, it seems as though the loss of CD133, and expression of VEC and vWF is important in the transformation of circulating EPCs into more mature ECs²³. This transformation is thought to occur while EPCs are still in circulation, but there is still debate as to exactly when EPCs fully differentiate into mature endothelial cells in vivo²³.
**Resistance Training**

Resistance training (RT) is a form of physical exercise that involves the use of any form of resistance to induce skeletal muscle contraction, which helps improve strength, size of skeletal muscle, metabolism, and overall health\textsuperscript{29}. RT commonly relies on the technique of progressively increasing the force output on target muscle groups through the use of a variety of equipment and exercises. The intensity, volume, and frequency of an exercise can be manipulated in order to achieve the desired changes in an individual. Lack of physical activity is associated with increased chances of developing CVD in a positive dose-response fashion\textsuperscript{30}. Physical inactivity promotes the release of bioactive mediators that alters coagulation and fibrinolysis, which increase the likelihood of endothelial dysfunction and atherosclerosis leading to CVD\textsuperscript{20}. RT has been shown to assist the body in burning calories via an increase in lean body mass and basal metabolism\textsuperscript{31}. Thus, resistance training exercise is a viable strategy for primary and secondary cardiovascular disease prevention. Table \textsuperscript{4}\textsuperscript{31} summarizes the benefits of resistance training. RT also has potential therapeutic uses for smokers. In pilot study examining RT as an aid to smoking cessation, results showed that the RT group had a higher abstinence rate compared with the control, which suggests that has RT can be used as a adjunctive strategy in smoke cessation\textsuperscript{32}.
Table 4: Comparison of Aerobic Endurance Training with Resistance Training on Various Health Variables. ↑ indicates values increase; ↓, values decrease; ↔, values remain unchanged; ↑↑ or ↓↓, small effect; ↑↑ or ↓↓, medium effect; ↑↑↑ or ↓↓↓, large effect; LBM, lean body mass; HDL, high-density lipoprotein cholesterol; and LDL, low-density lipoprotein cholesterol. (Source modified from Pollock et al., 2000)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone mineral density</td>
<td>↑↑</td>
</tr>
<tr>
<td>% Fat</td>
<td>↓</td>
</tr>
<tr>
<td>LBM</td>
<td>↑↑</td>
</tr>
<tr>
<td>Strength</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Glucose metabolism</td>
<td></td>
</tr>
<tr>
<td>Insulin response to glucose challenge</td>
<td>↓↓</td>
</tr>
<tr>
<td>Basal insulin levels</td>
<td>↓</td>
</tr>
<tr>
<td>Insulin sensitivity</td>
<td>↑↑</td>
</tr>
<tr>
<td>Serum lipids</td>
<td></td>
</tr>
<tr>
<td>HDL</td>
<td>↑↔</td>
</tr>
<tr>
<td>LDL</td>
<td>↓↔</td>
</tr>
<tr>
<td>Resting heart rate</td>
<td>↔</td>
</tr>
<tr>
<td>Stroke volume, resting and maximal</td>
<td>↔</td>
</tr>
<tr>
<td>Blood pressure at rest</td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>↔</td>
</tr>
<tr>
<td>Diastolic</td>
<td>↓↔</td>
</tr>
<tr>
<td>V̇ O₂ max</td>
<td>↑↔</td>
</tr>
<tr>
<td>Submaximal and maximal endurance time</td>
<td>↑↑</td>
</tr>
<tr>
<td>Basal metabolism</td>
<td>↑↑</td>
</tr>
</tbody>
</table>
METHODS

Study Participants

Subjects were recruited and screened using print advertisements, flyers, and internet postings from the West Los Angeles community. Twelve young adults (age 18-5) male and female light/moderate smokers (100 cigarettes lifetime minimum, 15 cigarettes per month minimum) were randomly assigned to either the resistance training group or control. Potential participants were excluded if they had documented CVD, cardiac arrhythmia or electrocardiogram (EKG) not conducive to arterial stiffness indices assessment, used medications that influence cardiovascular function, body composition or insulin indices in the prior 6 months, or exercised vigorously > 2 times a week. Patient data were excluded from the study if the participant did not complete the study.

On the day of testing, subjects fasted overnight and abstained from alcohol, caffeine, and vitamin supplements for 24 hours prior to the measurement. Subjects were asked not to engage in any moderate to vigorous physical activity within 36 hours of the visit. Smokers were also told to refrain from smoking after midnight on the day of scheduled visiting, with the time of their last cigarette recorded. Female visits were performed in the early follicular phase (days 1-7) of their menstrual cycle. All of the study protocols were approved by the University of California, Los Angeles (UCLA) Institutional Review Board and were performed according to the Declaration of Helsinki.
Smoking Dependence Assessment

To verify smoking dependence status, smokers were assessed using the Fagerström test for nicotine dependence (FTND). Figure 9 explains the guidelines for the Fagerström scoring interpretation. A score of 0-3 is considered to be a low level of smoking dependence, and is characterized by a mild physical dependence, potential benefit from professional counseling, and no recommendation of pharmacotherapy at initial assessment. A score of 4-6 points is characterized by medium physical dependence, a benefit from professional counseling, and possible treatment with pharmacotherapy after initial assessment. A score of 7-10 points is considered to be a high level of dependence. Participants scoring in this range show strong physical dependence, require professional counseling, and are recommended to undergo pharmacotherapy if suitable.

<table>
<thead>
<tr>
<th>TOTAL SCORE</th>
<th>LEVEL OF DEPENDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 3 points</td>
<td>Low</td>
</tr>
<tr>
<td>4 – 6 points</td>
<td>Medium</td>
</tr>
<tr>
<td>7 – 10 points</td>
<td>High</td>
</tr>
</tbody>
</table>

Figure 9: Fagerström Score Guideline. The level of smoking dependence was measured by the Fagerstrom questionnaire during visits 1 and 2.
Resistance Training

Training occurred at the John Wooden Recreation Center (UCLA). Participants engaged in three supervised 60-minute resistance-training sessions per week for twelve weeks. The training was split into three linear periodization phases. During phase 1 (week 1-2), participants were required to complete two sets of 12-15 repetitions for each exercise at their repetition maximum (RM). Repetition maximum is defined as reaching volitional fatigue/failure within the given repetitions. In phase 2 (week 3–7), participants completed three sets of 8–12 repetitions at their RM, and in phase 3 (week 8–12), participants completed six to eight repetitions at 100% at their RM. Weight of the exercises were increased to maintain the prescribed training intensity. Participants cycled between two workout regimens during their training sessions, which occurred on three nonconsecutive days per week. Workout 1 consisted of dumbbell (DB) squat, cable row, DB front lunge, DB row, barbell (BB) deadlift, DB triceps extension, and DB curls. Workout 2 consisted of DB step-up, BB chest press, machine squat, DB overhead press, DB incline chest press, DB side raise, DB reverse fly, and abdominal crunches. A certified personal trainer supervised all training sessions.
Before maximal strength testing, participants warmed up each muscle group by performing 8-10 repetitions of BB bench press, 45° incline leg press, and machine-seated row with weight equal to 40-60% of their estimated one repetition maximum (1-RM). Following the warm-up, maximal strength testing was carried out using the same exercises as during the warm-up but performed at there 100% 1-RM. In order to determine each participants 1-RM, weight was increased progressively while decreasing the repetitions until the participant could safely attempt an estimated 1-RM for each exercise. Participants were allowed 3–4 min of rest between all sets. All participants performed two maximal strength tests, one immediately preceding the first training session and the second immediately preceding their penultimate training session. All participants were asked not to perform RT exercises beyond the supervised sessions. Relative strength (RS) measures were calculated by dividing each measure [kilograms (kg)] by participant body weight (kg)\textsuperscript{33}.

**Outpatient Visit Procedures**

The measurements were taken from the participants at baseline (visit 1) and at the end of the study on week 13 (visit 2). Each measurement period consisted of two outpatient visits. The first visit was at the UCLA Clinical and Translation Research Center (CTRC). Participants had their CTRC outpatient visit within 72 hours after the last training session in order to control for any acute effects of the training program due to RT. The subsequent same-week Saturday visit occurred 96-120 hours following the last training session. Before each visit, participants
were reminded to: 1) avoid all moderate-to-vigorous physical activity 24 h before testing and 2) abstain from all food and drink (except water) for ~12 h before each visit. Verbal confirmation of adherence to the aforementioned criteria was obtained immediately before all testing. 

**Outpatient Visit 1**

Participants were instructed to arrive at 7:30 AM on the day of the visit, with each visit lasting approximately 3.5 hours. First, a physician administered a 12-lead ECG to potential participants in order to assess whether they were healthy enough to participate in exercise training. Measurements were carried in duplicates in all participants to ensure accuracy. Fasting blood samples were collected, and serum was separated and stored at −80°C until assayed. Subsequently, a two-hour oral glucose tolerance test (OGTT) was performed.

**Outpatient Visit 2**

The body compositions of participants were determined by a dual-energy X-ray absorptiometry scan (QDR 4500 fan beam X-ray densitometer; Hologic, Bedford, MA). Glycated hemoglobin A1c (HbA1c) was measured via a DCA Vantage analyzer (Siemens Medical Solutions USA, New York, NY), and a physical activity questionnaire [International Physical Activity Questionnaire (IPAQ)] was administered. After body composition scans were completed, a physician performed a muscle biopsy on the left vastus lateralis muscle.
Quantification of Endothelial Progenitor Cells (EPC)

Blood was collected from participants once before the start of the study and once after the study was completed. EPC were quantitated using a novel cytometry protocol we developed. Whole blood (10mL) was collected and erythrocytes were lysed. Following 10 min incubation, leukocytes were isolated by density gradient centrifugation, and then subsequently washed. A 7-color antibody panel was used to stain the population of leukocytes: anti-CD34-PE-Cy7, anti-CD-3, anti-CD-19, anti-CD-33, anti-FITC-CD45, anti-CD133-PE, and anti-APC-KDR. Acquired pellets were incubated with mouse serum for 20 min. Following a 45-min incubation, samples and fluorescence minus one tubes (FMOs) were washed with staining buffer (PBS + 3%FBS, 0.5% bovine serum albumin and 1% sodium azide). Propidium iodide was added for discrimination of dead cells. Samples were acquired on a BD LSR II flow cytometer. The mononuclear cell fraction was identified by forward scattering and low side scattering. A sequential gating strategy selecting live mononuclear cells with low expression of CD45 led to quantification of CD34⁺, CD133⁺, KDR⁺ and CD133⁺KDR⁺ events.
RESULTS

Measurements Within RT Group

The mean age was 27.1 years old (SD=6.6) in the RT group. Participants scored an average of 4.0 (SD=2.82) on the FTND at baseline (Table 5). We observed a 54% decrease (P=0.19) in FTND score after resistance training intervention in RT. The average RS at baseline was 3.89 (SD=0.69) and increased 23% to 4.77 (SD=1.03) in visit 2 (Table 6). Average weight at baseline was 71.9 kg (SD=9.3), and there was no significant increase in weight measured in visit 2. The mean body mass index (BMI) was 25.9 kg/m² (SD=4.1) during baseline and 26.2 kg/m² (SD=3.9) during visit 2.

Table 5: Achieved Fagerström Test for Nicotine Dependence Score in Resistance Training during Visit 1 and Visit 2.

<table>
<thead>
<tr>
<th></th>
<th>Visit 1</th>
<th>Visit 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean</strong></td>
<td>3.89</td>
<td>4.77</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>0.69</td>
<td>1.03</td>
</tr>
</tbody>
</table>
We defined circulating EPCs as cells that express CD34+, CD133+, and KDR+.
There was a decrease in the absolute number of circulating CD34+, KDR+, and CD133+ after RT intervention. Furthermore, we observed a decrease in the percentages of KDR+ of CD34+ (%KDR+/CD34+) and CD133+ of CD34+ (%CD133+/CD34) from baseline. Table 7 is a summary of the observed changes in EPCs in peripheral blood of RT.

Table 7: Summary of Changes in Endothelial Progenitor Cells of Resistance Training.
Values are expressed as means with ± standard error of the mean (SEM)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Changes</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD34+ (/ml blood)</td>
<td>1424.83±483.69</td>
<td>485.33±114.32</td>
<td>-939.50</td>
<td>0.09</td>
</tr>
<tr>
<td>CD133+ (/ml blood)</td>
<td>675.83±218.21</td>
<td>176.16±39.28</td>
<td>-499.66</td>
<td>0.08</td>
</tr>
<tr>
<td>KDR (/ml blood)</td>
<td>11.16±4.28</td>
<td>2.33±0.80</td>
<td>-8.83</td>
<td>0.12</td>
</tr>
<tr>
<td>%CD133+ of CD34+</td>
<td>48.32±2.52</td>
<td>41.02±7.11</td>
<td>-7.29</td>
<td>0.21</td>
</tr>
<tr>
<td>%KDR+ of CD34+</td>
<td>0.68±0.18</td>
<td>0.50±0.13</td>
<td>-0.18</td>
<td>0.49</td>
</tr>
</tbody>
</table>
Measurements Within Control

The average age of participants in the control group was 27.1 years old (SD=5.2). Average weight at baseline was 82.0 kg (SD=16.0), with no significant change in visit 2. Average BMI at baseline was 27.6 kg/m$^2$ (SD=5.9) and 27.2 kg/m$^2$ (SD=6.2) at the end of the study. The mean FTND score at baseline was 2.83 (SD=2.64) and increased 18% to 3.33 (SD=2.58) by visit 2 (Table 8). The average RM score at baseline was 5.09 (SD=0.54) and 4.58 (SD=1.05) at visit 2 (Table 9).

Table 8: Achieved Fagerström Test for Nicotine Dependence Score in Control During Visit 1 and Visit 2

<table>
<thead>
<tr>
<th>FTND Measurements</th>
<th>Visit 1</th>
<th>Visit 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean</strong></td>
<td>2.83</td>
<td>3.33</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>2.64</td>
<td>2.58</td>
</tr>
</tbody>
</table>

Table 9: Repetition Maximum Measured in Control during Visit 1 and Visit 2

<table>
<thead>
<tr>
<th>RS Measurements</th>
<th>Visit 1</th>
<th>Visit 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean</strong></td>
<td>5.09</td>
<td>4.58</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>0.54</td>
<td>1.05</td>
</tr>
</tbody>
</table>
There was a mean decrease in CD34+, CD133+, and KDR from baseline measurements. Furthermore, we observed a decrease in %CD133+/CD34+ and %KDR/CD34+. Table 10 shows a summary of the changes in EPC measurements in the control group.

Table 10: Summary of Endothelial Progenitor Cell Changes in Control. Values are expressed as means with ±SEM.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Changes</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD34+ (/ml blood)</td>
<td>744.50±175.34</td>
<td>361.50±85.53</td>
<td>-383</td>
<td>0.18</td>
</tr>
<tr>
<td>CD133+ (/ml blood)</td>
<td>313.66±54.76</td>
<td>119.83±58.37</td>
<td>-193.83</td>
<td>0.09</td>
</tr>
<tr>
<td>KDR (/ml blood)</td>
<td>12.83±7.29</td>
<td>3.00±1.61</td>
<td>-9.83</td>
<td>0.25</td>
</tr>
<tr>
<td>%CD133+ofCD34+</td>
<td>47.16±4.38</td>
<td>26.15±9.14</td>
<td>-21.01</td>
<td>0.05</td>
</tr>
<tr>
<td>%KDR+ofCD34+</td>
<td>1.27±0.57</td>
<td>0.89±0.31</td>
<td>-0.38</td>
<td>0.41</td>
</tr>
</tbody>
</table>

Measurements Between Resistance Training and Control

RT had a 91% mean increase in CD34+ (/ml of blood) compared with control at baseline. CD133+ count (/ml of blood) was also 115% higher in RT compared to control at baseline. CD133+ and CD34+ (/ml of blood) were reduced in both groups from baseline, with CD34+ (/ml of blood) decreasing by an average of 66% in RT and 51% in control (OR 2.5, 95% CI= 0.16-38.60), as shown in Figure 10. As illustrated in Figure 11, we observed a mean decrease in CD133+ (/ml of blood) by 74% in RT compared to 62% in control (OR 2.5, 95% CI= 0.16-38.60).
**Figure 10:** CD34+ Measurements in Resistance Training Versus Control During Visit 1 and Visit 2. Data end points are depicted as average values collected at each visit.

**Figure 11:** CD133+ Measurements in Resistance Training Versus Control during Visit 1 and Visit 2. Data end points are depicted as average values collected at each visit.
The average KDR amount (/ml of blood) was 13% higher at baseline in control compared to RT. In visit 2, there was a similar decrease in measured KDR (/ml of blood) for both groups, with a decrease by 77% in control and 79% in RT (OR 10.0, 95% CI= 0.64-154.40). Figure 12 illustrates the comparison of KDR measurements at baseline and visit 2 for RT and control.

Figure 12: KDR Measurements in Resistance Training and Control at Visit 1 and Visit 2. Data end points are depicted as average values collected at each visit.

Compared to control at baseline, RT had a 41% higher mean score on FTND. RT participants had an average 45% mean decrease in FTND score by visit 2, while control participants showed an 18% average increase (OR 0.08, 95% CI= 0.24-0.31).
0.002 to 2.244). Based on the FTND scoring guidelines, 4 participants in RT were considered to have low nicotine dependence (achieving a score of 0-3 on FTND questionnaire), while 2 of the participants were considered to have high nicotine dependence (achieving a score of 7-10 on FTND questionnaire) at baseline. Furthermore, control had 4 participants with low nicotine dependence, 1 with medium nicotine dependence, and 1 with high nicotine dependence at baseline. By the assessment in visit 2, 4 of the 6 participants in RT continued to have low nicotine dependence, while 2 had become medium nicotine dependent. In the control group at visit 2, 3 participants were low nicotine dependent, 2 were medium nicotine dependent, and 1 was highly nicotine dependent. Figure 13 depicts the average achieved FTND score for RT and control at baseline and visit 2.
Following RT intervention, participants in RT showed a 22% mean increase in RS compared with a 10% decrease in control (OR 0.138, 95% CI= 0.005-3.627). There was no significant difference in measured BMI between RT and control during visit 1 and 2.
DISCUSSION

The implications based on the results from this study do not suggest that there is a positive correlation between RT intervention and EPC count in young smokers. It should be noted that EPC count decreased in both RT and control from baseline. There are several possible explanations for how atherosclerotic risk factors can influence the number of EPCs. One scenario might be an increased apoptosis of premature progenitor cells. For example, it has been shown that immature EPCs are sensitive to angiostatin, which is a naturally occurring protein in humans, and induces apoptosis in CD34+ EPCs\textsuperscript{34}. Another possible scenario is that participants continued to smoke throughout the study. Smoke cessation was not a part of the inclusion criteria for this study (with the exception of visit day 1 and 2), therefore the reduced EPC count in both groups might be explained by the oxidative stress caused by smoking, which is a well-established inducer of apoptosis\textsuperscript{35}. Of the three markers to identify EPCs, KDR experienced the largest proportional decrease from baseline compared to CD34+ and CD133+. The reduction in KDR may be an important event in the overall decrease of circulating EPCs, as seen in our study. KDR is mediated by a signaling protein called vascular endothelial growth factor (VEGF), which is involved with vasculogenesis and angiogenesis\textsuperscript{36}. VEGF induces mobilization of EPCs towards vascular injury; however, EPCs in smokers show an impairment of chemotaxis despite the presence of VEGF\textsuperscript{24}. These findings suggest that
cigarette smoking reduces EPCs mobility, possibly through a decreased expression of KDR. Therefore, the proportionally larger decrease in KDR observed in our study may offer another explanation for the overall decrease in the total EPC count for both RT and control.

**Limitations**

An important limitation to this study was the small sample size. However, some of our findings are consistent with previous work on endothelial dysfunction and exposure to cigarette smoke\(^3^7\). Therefore, a future study with an adequately powered experimental design is warranted. Moreover, we were unable to match for age, gender, and smoking status in our control group due to the low sample size. This would inevitably introduce confounding variables, which is reflected by the relatively large confidence intervals reported in our study.

Another possible limitation to our study was how we chose to define circulating EPCs. The use of EPCs as a biomarker is still relatively new, and their specific functions are still unknown. Furthermore, there has yet to be a single biomarker identified that can accurately recognize a circulating EPC *in vivo*. Because of this, there are various definitions and characterizations of true EPCs. Our methods relied on identifying three surface markers (CD133+, CD34+, and KDR). However, CD34+ has also been shown to be present on non-hematopoietic cells such as muscle satellite cells, corneal keratocytes, interstitial cells, and epithelial
progenitors\textsuperscript{38}. In spite of this, CD34+ is still widely used as one of markers for EPCs. Therefore, there should be agreement in the scientific community on the characterization of EPCs and its subtypes. This will allow for a more systematic approach to understanding the role of EPCs.
LIST OF JOURNAL ABBREVIATIONS

Am J Public Health ........................................ American Journal of Public Health
ATVB ................................................ Arteriosclerosis, Thrombosis, and Vascular Biology
Cancer Res ....................................................... Cancer Research
Circ Res ........................................................ Circulation Research
Int J Epidemiol ........................................ International Journal of Epidemiology
J Am Coll Cardiol ........................................... Journal of the American College of Cardiology
J Appl Physiol ................................................ Journal of Applied Physiology
J Natl Cancer Inst ........................................... Journal of the National Cancer Institute
JAMA ......................................................... Journal of the American Medical Association
MMWR .......................................................... Morbid Mortal Weekly Report
Nicotine Tob Res .............................................. Nicotine Tobacco Research
Nitric Oxide Biol Chem ....................................... Nitric Oxide: Biology and Chemistry
Smok Tob Use .................................................... Smoking and Tobacco Use
Vasc Health Risk Manag .................................... Vascular Health Risk Management
REFERENCES


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CURRICULUM VITAE

ANDREW T. DAM

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E-mail: andrew.dam1@gmail.com
Address: 836 11th Street, Manhattan Beach CA, 90266
Born: 1991

EDUCATION

Boston University School of Medicine, Boston
Master’s in Medical Science Student August 2013- Present
Course Work Complete Spring 2014
Thesis Completion Expected Spring 2015

University of California, Irvine Sept. 2009- June 2013
Bachelor of Science, Biological Sciences

RESEARCH EXPERIENCE

Exercise Physiology and Metabolic Disease Lab June 2014-Present
Dr. Christian Roberts
Graduate Research Assistant
University of California, Los Angeles, CA
- Responsible for isolating endothelial progenitor cells and other bio
  markers from blood samples
- Carrying out Flow Meter Dilation (FMD) protocols within a clinical setting
- Exposed to constant patient contact in the Clinical & Translational
  Research Center
- Administering Constant Glucose Monitors
- Proficient in handling YSI glucose analyzer

Neuropharmacology Lab Research June 2011- June 2013
Dr. Frances Leslie Lab
Undergraduate Research Assistant
Department of Pharmacology, University of California, Irvine
- Over 600 hours of lab experience modeling early tobacco exposure in
  teenagers using rat models of adolescent nicotine exposure
- Conducted an investigation, using rat models of adolescent nicotine
  exposure, to determine whether spatial discrimination was due to the
  novelty of an object or altered function of the dentate gyrus
- Project funded through UROP proposal: Examining the effects of
  nicotine pretreatment on novel-object discrimination in adolescent and
  adult rats
CIVIC ENGAGEMENT

Mission Hospital Auxiliary Program  
*Volunteer*  
St. Joseph Mission Hospital, Laguna Beach, California  
March-Sept. 2012  
- Promoted smooth operation in emergency room by assisting doctors and nurses in delivering blood and urine samples to laboratory facility, organizing outpatient reports, preparing and cleaning examination rooms, constructing intravenous and blood-sample kits  
- Interacted with patients to facilitate their well-being by providing blankets, food, water, and other amenities  
- Kept hospital rooms properly stocked in between medical examinations  
- Observed doctors and nurses collecting medical histories, evaluating psychiatric disorders, performing triage, prescribing medical treatments, and providing diagnostic testing of blood, urine, and CT scans

Project Vietnam Foundation  
*Medical Mission Volunteer*  
Vietnam  
Summer 2010  
- Assisted doctors and a team of over 60 undergraduate, medical school, and residency students in providing over 4000 locals with medical, eye, and dental screenings  
- Administered basic clinical assessments, most notably: measuring blood pressure, pulse, height and weight, and collecting patient medical histories  
- Provided medication and healthcare services to six different underserved provinces

SHADOWING

Physical Medicine & Rehabilitation Department  
Kim D. Thai, SCPMG Regional Chief Physician, PM&R  
*Shadow/ Volunteer*  
Kaiser Permanente, Baldwin Park, CA  
May 2014- Present  
- Exposed to manual medicine techniques that emphasize myofascial pain, e.g., myofascial release on patients with chronic and acute pain.  
- Assist Dr. Kim in performing Pain Questionnaires Surveys for his lower back pain research  
- Gained a better understanding of the physical and emotional needs required from those suffering from chronic and acute pain  
- Help Dr. Kim administratively by assisting his patients make and confirm future appointments  
- Work alongside team of physical and occupational therapists, psychologists, and nurses
LEADERSHIP

**Phi Kappa Psi Fraternity**

*Executive Board Member*

University of California, Irvine, CA

- Member of the executive board that manages and maintains an organization with over 60 chapter members
- Organized the Comedy Show for Breast Cancer fundraiser, which resulted in raising over $6000 and proceeds donated to the American Cancer Society
- Organized a philanthropic effort that contributed 500 total volunteer hours with the Boys and Girls Club of America

**American Leadership Academy**

Cabo San Lucas, MX

- Participated in 7 seminars developing leadership, communication, and commitment skills
- Participated in team-building exercises with successful and dynamic leaders in business, law, public service, education, science & technology, and sports
- Planned and implemented a lecture, titled “Learn, Return, & Lead” for over 100 undergraduate students to increase involvement in leadership on & off campus

EMPLOYMENT

**Anteater Recreation Center**

*Fitlab Employee*

University of California, Irvine, CA

- CPR and First Aid certified to ensure safety and well being of patrons in the weight rooms
- Trained incoming staff to exhibit strong patron relations by emphasizing personal communication skills as well taking initiative in work duties
- Maintained a comfortable and optimal environment in the gym by cleaning equipment and organization of weight equipment

HONORS & AWARDS

**Douglas White Oaks Ranch Scholarship**

The Boeing Company, El Segundo, CA

- Recipient of $5000 scholarship in recognition of leadership and academia

**Dean’s Honor List**

University of California, Irvine, CA

- Received Dean’s Honor List fall, winter, and spring quarter of junior year, and winter quarter of senior year