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Comparison of Cardiovascular Risk Factors in Deployed Military Personnel



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# Comparison of Cardiovascular Risk Factors in Deployed Military Personnel

by

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DISSERTATION

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Dedication

*"Men sleep peacefully in their beds at night because rough men stand ready to do violence on their behalf*." *George Orwell*

This dissertation is dedicated to all the service men and women who are deployed in support of the Global War on Terror, especially to my husband, Joseph "Jake" McGraw, currently commanding Bravo Company, 3rd Battalion, 1st Special Forces Group (Airborne) in Iraq. These brave men and women are sacrificing their lives and time with their families to protect the freedoms that we enjoy as a nation.

Acknowledgements

In September 2005, I was a military officer, the wife of a military officer, the mother of two small children, and pregnant with our third child; adding the role of "doctoral student" was a bit daunting. The last 3 years have been stimulating, exciting, and of course challenging at times. When I found out my husband was scheduled to deploy to Iraq during my last year as I was completing my dissertation, I simply had to take a big breath in and repeat to myself, "I can do this".

As a parent, I reflect upon the innumerable books I have read to my children each night over the years. In the organized chaos of our routines, settling down to read with the children allows me to see the parallels in my life and that of storybook characters. From Seuss's "Oh, the Places You'll Go" to "Green Eggs and Ham", there seems to be a message I can apply to my own life. One of their favorite books is "Let's Be Thankful": a book with a simple message but a message that is enormously applicable in life. I am thankful to God for the blessing of friends, family, and colleagues who have supported me during this journey. I arrived at this point only through enormous help from so many people, too many to name. I could not have completed my dissertation without the support of many people who have played key roles in the process from a personal, professional and logistical standpoint.

Words cannot adequately express how grateful I am to my amazing, beautiful family for their unending support during my doctoral studies. My children, Katie, Tommy, and Sydney are the joys of my life. Despite spending countless nights away from them when I traveled to San Francisco, they were satisfied with a goodnight kiss

through the phone. Katie often brought a smile to my face when she would draw me a picture and insisted I bring it to school “to show all (my) friends”. And I did. Tommy has boundless energy that is awe-inspiring with a memory that is remarkable. He often reminded me of things that needed to be done, which I valued, especially during this last, extraordinarily busy year. Sydney’s growth and development mirror my travels through the doctoral program. When I started the program she was a vision, a dream; we did not know her and could only imagine life with her. Since I have been in the program, she has developed into a walking, talking, and quite passionate toddler. What growth! My husband, Jake, is my “rock”. He has been nothing but supportive of my endeavor, even during the most chaotic times, and he often sacrificed his own personal goals to help me achieve mine. He still offers support from 6700 miles away; I am thankful for his unending support and love for our gorgeous children and me. I could not have done this without him and I am forever grateful.

My academic advisor, Dr. Kathy Dracup has been inspirational as both personal and professional mentor. Kathy has shown compassion and understanding as I sometimes struggled to balance the competing requirements of parenthood and a doctoral program; she often reminded me to have realistic expectations of myself. Over the course of my studies, she was there when I needed someone to hold my hand, and sometimes I clung on for dear life. More often, however, she would let go and give me freedom to develop my ideas as I ventured into unfamiliar territory: the dissertation. Knowing she never lost sight of me and was only an email or phone call away gave me

confidence to develop as a researcher. Undoubtedly, this gift of self-confidence will be a great asset as I embark on my new career as a researcher in the Army.

Dr. [Colonel (ret)] Barb Turner has been a friend and professional mentor to me for over 12 years. As I contemplated what next step to take in my military career, I called her. She nudged me in the direction of a doctoral program. I was not sure I could do it—she convinced me that I could and absolutely should take this step. Thanks to her, I have truly found my niche in nursing. Barb has been a great source of personal and professional support through both difficult and rewarding times, and I strive to follow her example.

I am grateful to Dr. Nancy Stotts for giving me direction at a critical point in the doctoral program. Her quick and thorough paper edits were invaluable, as was her involvement during the journey through my doctoral study.

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My access to Dr. Steven Paul was limitless as I worked on the statistical analysis for my project. His flexibility with his schedule during my "commutes" to San Francisco and his constant assistance via phone and email was invaluable. His willingness to help

me with the finer details of my analysis was critical to ensure the results of my studies were sound.

The funding for my dissertation was critical, and I am grateful to be a 2007 Sayer Memorial Fund Scholar (American Nurses Foundation), and the recipient of the Uniformed Nurse Practitioners Association Doctoral Dissertation Grant (American Academy of Nurse Practitioners) and the University of California, San Francisco Graduate Dean's Health Sciences Fellowship. Without funds, I could not carry out this study. Many players assisted me to ensure my research project came to fruition. At Madigan Army Medical Center, Dr. Lori Loan worked with me very early in the project development to make certain I had everything I needed from both a logistical and administrative standpoint. Dr.'s Loan and Mary McCarthy were a great source of support to me as I navigated the waters of project development and the Institutional Review Board. Kathi Hamilton's smiling face was always a welcome sight in the Nursing Research office, and I appreciate all she has done to keep me administratively straight! Other key players at Madigan who helped me with my research study include Captains Michael Hartenstein, PhD and Holly Bryant, JD, Jim Wright, and Tammy Cortez. At the Soldier Readiness Processing Site, I am grateful to all of the staff who added to the terrific experience with my daily interactions with them, but especially to Andrea Madison and Jim Brassard for supporting this study and providing me with space and the access to the Soldiers who made this study successful. Aaron Johnson frequently assisted with blood draws, especially the "difficult sticks" and his administrative support was invaluable. His humor at the SRP site made the days fun.

At Landstuhl Army Medical Center, Captain Ann Ketz expertly orchestrated the administrative and logistical requirements prior to my arrival. Not knowing me, she went above all expectations. Once my feet were on the ground in Landstuhl, Captain Brian Van Hall helped me navigate my way through the halls of the medical center and went out of his way daily to make sure I had everything I needed. In the Patient Administration Division, Mr. Ralf Mayer was unrelenting in helping me track down lists and charts so I could obtain my full sample in Phase I. Despite the large number of charts I kept requesting, he found them with a smile, even when it meant transporting them from a very remote site.

Most importantly, I am grateful to each soldier who volunteered for this study. Without their willingness to participate, I would not have been able to complete my dissertation. These combat veterans are true American heroes.

Comparison of Cardiovascular Risk Factors in Deployed Military Personnel

Leigh K. McGraw

## Abstract

Acute cardiovascular (CV) events occur in deployed military personnel yet little is known about the CV risk profile of deployed U.S. military service members who experience ACS. Stress as a potential confounder of CV events in service members deployed in the ongoing Global War on Terror (GWOT) has not been addressed.

The primary aim of this dissertation was to use a case-control design to compare CV risk factors between a group of 93 service members deployed in support of the GWOT who experienced acute coronary syndromes (ACS) and 136 rank, area of operations, and ethnicity-matched controls who did not experience ACS while deployed in support of GWOT. The matching variables controlled for the confounding effects of SES, stress, and ethnicity.

Of the 93 ACS cases, 81.7% had an acute myocardial infarction and 18.3% had unstable angina. Most major CV risk factors were significantly different between the two groups except blood sugar and history of dyslipidemia. In a univariate conditional logistic regression model, all CV risk factors except blood sugar were significant predictors of ACS. In a multivariate logistic regression model, higher age [1.24 (1.11, 1.40)], higher total cholesterol/high density lipoprotein cholesterol ratio [2.85 (1.65, 4.93)], and family history of premature coronary artery disease [4.93 (1.66, 14.64)] remained significant independent predictors of ACS in service personnel deployed

overseas in the GWOT. Both groups had Framingham risk scores that categorized them as “low risk”.

Improved CV health surveillance programs are needed in the military population to identify those with multiple CV risk factors. Interventions to reduce CV risk in military service members, especially prior to an overseas deployment, are essential. Based on the findings of this study, additional biomarkers that enhance the predictive ability of the Framingham risk score must be sought to improve a clinician’s ability to stratify cardiac risk in young military men.

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## Chapter 1

### Introduction

Military medicine is somewhat of a dichotomy. As military health care providers, we are both protectors and providers. We have ongoing proficiency training and assessments in both the use of weapons that are issued to us in combat as well as the skills required to care for the physical and psychological wounds those very weapons inflict upon our fellow service members. These two competencies are seemingly contradictory, but they define the core of military medicine. In my own experience, another characteristic of this unique blend is added—one that so many Americans are familiar with—the Army nurse. Army nurses, whether represented by World War II prisoners of war or those depicted in television and films that cross generations, are the compassionate, yet tough-as-nails soldier-providers who above all things, care for *their guys*. It is not an assumed identity, but rather one that develops over years of treating a very special patient population that is more often ready to face bullets than request medical treatment. We are fiercely loyal to them and passionate about the care of *our guys*, whether those "*guys*" are men or women, officers or enlisted, young recruits or retired veterans—even if it means side-stepping our own institutional bureaucracy at times.

The research that follows is one single attempt to take care of our service members. In my work as an Army family nurse practitioner, I became increasingly aware of the prevalence of obesity in soldiers as well as the young men who retired with several major cardiovascular risk factors, many identified for the first time as they exited

the service. Patients frequently told me that time was a limiting factor for employment of preventive health measures, and only upon retirement did they take the time to address health concerns. As a nation at war, I naturally had to wonder about the vulnerability of an individual who dismissed preventive health care, specifically cardiovascular health care, and possibly deployed with several cardiovascular risk factors to a sometimes austere and often stressful combat environment.

The retired veterans we care for represent the best of our generations, while the young men and women we prepare for war—and treat during and after—represent the best of what and who we will be as a nation. We have an obligation to ensure their medical needs are met, not only from a treatment perspective, but also in the realm of preventive medicine. My study deals directly with how we as an Army, as medical professionals, and as nation can better take of the military servicemen—*my guys*.

## Background

Military health, to include coronary healthy, is an important factor in service member and unit readiness and is a critical component of our national defense. Though cardiovascular disease (CVD) is relatively rare in the military population, a cardiovascular (CV) event in a deployed individual can have catastrophic effects on the individual and affect the unit's mission readiness. Occurrence of acute coronary syndrome (ACS) in a military force that must be healthy and physically capable to operate in the current Global War on Terror is concerning.

The commonly held perception of military service members is one of youth and vitality. Military members benefit from the inclusion of a physical training period as part of their workday. Most military personnel are young, engage in regular vigorous

physical activity; being a part of the military is contingent upon acceptable physical fitness and weight and for these reasons, members of the military are regarded as the epitome of health. While youth and healthy lifestyles reduce the risk of cardiovascular disease (CVD), military personnel still exhibit worrisome trends of increasing overweight, obesity, and smoking. Impressive rates of other cardiovascular (CV) risk factors are also present in the military population, and as the force ages, the prevalence of CV risk factors will only continue to increase.

Few researchers have explored CV risk and CVD in the military population. Evidence exists that CV events occur in deployed military personnel (Filardo et al., 2005; Sullenberger & Gentlesk, 2008); however, the research on the impact of specific war stressors and CVD is limited to civilian populations. The research on stress and deployed personnel focuses on the negative psychological sequelae of combat, most notably, posttraumatic stress disorder. Conspicuously missing from the body of evidence are the physiological sequelae of prolonged stress. Undoubtedly, counter-terrorism and counter-insurgency operations are complex, and the very nature of this type of combat results in lengthy campaigns. The GWOT requires the deployment of service personnel into these difficult environments, often multiple times. The long deployments are punctuated by acutely stressful events such as indirect fire and attacks by improvised explosive devices.

The acknowledgement of the physical and psychological stress created by the counter-insurgency and counter-terrorism environment suggests that a thorough understanding of a service member's CV fitness take place prior to deployment. The

relationship between CVD and traditional CV risk factors coupled with acute and chronic stress exposure during military deployments cannot be completely ignored. The U.S. government calls upon individuals to put themselves at risk for prolonged periods in stressful combat situations and successful operational outcomes and care of military personnel demands investigation of any relationship between stress and CVD. The purpose of this dissertation is to begin to explore this relationship by examining a sample of deployed military personnel who experienced ACS and comparing them to a healthy population returning from deployment who did not experience ACS.

## Theoretical Framework

Pathophysiologic theory provides the framework for the dissertation. The pathophysiology of both atherosclerosis and insulin resistance are paramount in the development of atherosclerosis and CVD; however, the physiologic response to stress must be considered in risk assessment for CV events in military personnel deployed overseas in support of GWOT. Figure 1 depicts the proposed relationship between traditional risk factors, emerging risk factors, and stress with CV risk and acute CV events.

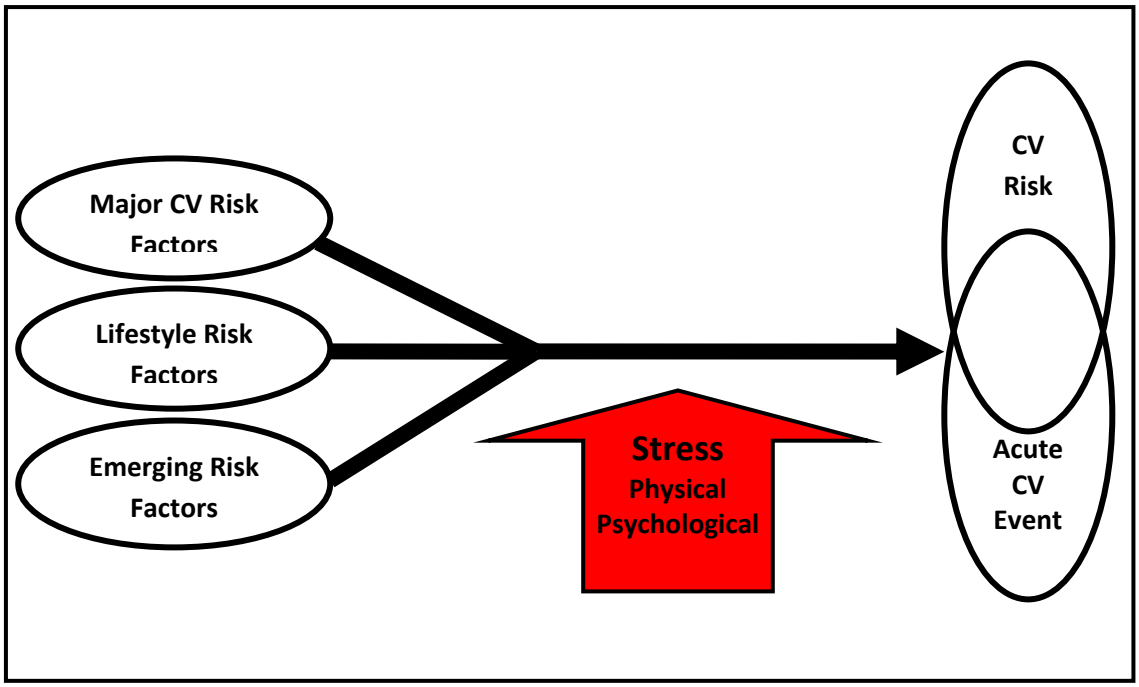


**Figure 1 Theoretical framework of CVD in Deployed Military Personnel**

Major risk factors include age, family history of premature coronary artery disease, low high-density lipoprotein cholesterol, hypertension, and smoking. Lifestyle risk factors include sedentary lifestyle and overweight and obesity; the concept of subclinical atherosclerosis, impaired fasting glucose, lipoprotein (a), proinflammatory factors, prothrombotic factors, and homcysteine are termed, "emerging risk factors" (NCEP/ATP III, 2001). Physiologic changes that occur as a result of exposure to acute or chronic psychological stress or physical stress may result in changes in an individual's risk factor profile or in a susceptible individual, result in the occurrence of a CV event.

## Dissertation Aims

The overall aim of the dissertation study is to identify CV risk factors in military personnel who are deployed in the ongoing Global War on Terror. This dissertation is divided into 5 chapters.

Chapter 1 is the introduction of the dissertation, and the overview, a brief background and the theoretical framework of the dissertation is described.

Chapter 2 is an overview of coronary artery disease in younger age groups and the prevalence of risk factors in the military population. With increases in current military operations in an acutely stressful environment, the role of stress and relationships to CVD are also examined.

In Chapter 3, the physiologic processes related to CV disease are reviewed, specifically atherosclerosis and insulin resistance. Physiologic responses to stress and their relationship to CV risk and CVD are also presented.

Chapter 4 is a comprehensive review of methods for global CV risk, comparing several tools for risk assessment. The methods of measurements of individual CV risk factor components contained in many of the tools in global risk assessment are discussed, including blood pressure, obesity, lipid parameters, alterations in glucose metabolism, insulin resistance, and self-report measures. The paper concludes with an evaluation of the Global War on Terror Stress Score, a composite score used to measure combat stress in deployed military personnel using screening questions currently used upon redeployment from the GWOT.

Chapter 5 is a descriptive research study on the CV risk factors present in a group of 100 men deployed in the GWOT who experienced ACS. Though the results are from a retrospective record review, it is the first study to identify and quantify specific CV risk factors of U.S. service members deployed in the GWOT, all with a definitive diagnosis of ACS.

Chapter 6 is a case-control research study, comparing traditional CV risk factors in military personnel deployed overseas in the GWOT who experienced ACS with those who deployed overseas in the GWOT who did not experience ACS. The participants were matched on rank, area of operations, and ethnicity to control for the potentially confounding effects of socioeconomic status, stress, and the well-documented differences in CVD and ethnic groups.

Chapter 7 summarizes the findings of the research studies and the implications for clinical practice, health policy on preventive health screening in military populations, and recommendations for future studies.

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A Review of Cardiovascular Risk Factors in U.S. Military Personnel

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## Introduction

Current military operations necessitate frequent mobilizations, and it is imperative that both the active and reserve force remain healthy and able to carry out their assigned military duties. A physically fit, combat ready military force must be prepared to deploy with short notice to engage in current and emerging conflicts worldwide. The mission readiness of the unit and the individual are affected by a service member's cardiovascular (CV) health. An acute CV event in a deployed individual poses a significant threat to mission success and a financial burden to the U.S. government not only for loss of trained personnel and equipment [1] but also for evacuation and treatment. It is crucial to determine accurately the presence of CV risk in military personnel to prevent potentially catastrophic CV events at a time of increased operational requirements.

This review focuses on cardiovascular disease (CVD) in young populations and CVD risk factors in the military population. Age, male gender, hypertension, dyslipidemia, smoking, obesity, glucose abnormalities, insulin resistance and the role of stress in CVD will be examined.

## Coronary Artery Disease

Cardiovascular disease occurs in individuals with multiple cardiac risk factors,[2] so it is crucial for health care providers to provide primary prevention activities to prevent the progression of CVD. Given the association of obesity and CVD, [3] and an increasing prevalence of overweight and obesity in the military population,[4] CV risk or CVD may well be increasing in what should be a young, healthy population. Table 1 compares risk

factor prevalence in military and civilian cohort studies. Civilian cohort studies may reflect trends seen in the reserve population, who are civilians mobilized for training or deployments.

*Coronary Artery Disease in the Young*

Young cohorts of civilians have been studied for the presence of CV risk factors. In both the Muscatine Study [5] and the Bogalusa Study [6] CV risk factors in childhood predicted development of CV risk in young adulthood. Analysis of postmortem data in a

| | **Military (%)** | **Civilian (%)** |
|---|---|---|
| **Hypertension** | 12.1[7] – 38 [8] | 7.2 - 30.1* [9] |
| **Dyslipidemia/Hypercholesterolemia** | 17.7 [10] - 31 [8] | 35.8- 64.7† [11] |
| **Smoking** | 32.2 [7] | 21.6 [12] |
| **Glucose abnormalities** | 3.2[13]-7 [8] | 18.3 - 39.7‡ [14] |
| **Overweight/Obesity** | 55.3 - 65.9§ [7] | 57.6 - 68‡ [15] |
| **Hyperinsulinemia** | 8.9 [16] | 34.8 [17] |

*Range represents prevalence in individuals 18-39 years and 40-59 years
†Range represents prevalence in males 20-34 years and 45-54 years
‡Range represents prevalence in individuals 20-39 years and 40-59 years
§Range represents services with the lowest (Marines) and highest (Navy) percentage of personnel $\geq$ 20 years with a BMI $\geq$ 25

**Table 1. Comparison of cardiovascular risk factors in military and civilian cohort studies**

multi-center study of 15 to 34 year olds who died from non-cardiac causes sought

identification of risk factors for atherosclerosis in young people.[7] In one study from this sample, over 10% of young men and 7% of young women had vulnerable plaques at risk to rupture in one or both of the coronary arteries examined, with the presence increasing with age.[8] The findings confirm atherosclerotic lesions start and progress at a young age and are associated with traditional CV risk factors. This study was particularly unique because CV risk factor assessment focuses on adults 30 years and older, based on the ages captured in the Framingham risk score (FRS).

Coronary artery disease (CAD) is documented in young military personnel. [9] Landmark research was published by Enos and colleagues [10] showing CAD in young Korean War combat casualties (mean age 22.1). In this very young sample (N=300), 77.3% had evidence of atherosclerosis and 65% had plaques causing luminal narrowing from 10 to 100%. A similar study was conducted on Vietnam War combat casualties (N=105), and though the mean age of the subjects was the same, only 45% were noted to have atherosclerosis.[11] Despite the difference in prevalence, both studies demonstrate the pervasiveness of CAD among young, presumably physically fit service members.

*Physical Exertion and CAD*

Among active duty service personnel, 57.6% engage in vigorous physical activity for 20 minutes 3 days per week.[4] Despite the fact that engaging in regular physical activity modifies an individual's CV risk, vigorous physical activity may play a role in the development of acute coronary syndrome (ACS).[12, 13] One mechanism which initiates the cascade of events associated with an acute cardiac event is rupture of a vulnerable

plaque; [14, 15]it is conceivable that physical exertion may play a role in cardiac events of military members whose job often includes physically demanding requirements. In a study of postmortem heart examinations, researchers showed significantly more frequent plaque ruptures in those who died from an acute myocardial infarction (AMI) during exertion when compared to those at rest.[12] Cardiac events were examined in firefighters in a case-control study and they were 64 times more likely to have a cardiac event while engaged in fire suppression, a strenuous and stressful duty, than those engaged in fire house or non-emergent duties.[13]

Occupational requirements of military personnel pose physical and psychological demands that may lead to an increase in CAD or even result in sudden cardiac death; for example, 39% (n=83) of exercise-related deaths in the military between 1996 and 1999 were related to CAD.[16] Furthermore, "undetermined sudden death" in service members over the age of 40 were likely the result of CAD, increasing the overall rate to 48% (n=104). Indeed, ACS has been documented in both Iraq[9] and Afghanistan (personal communication, Elizabeth Bridges, PhD, August 2, 2007). Exogenous factors contributing to ACS in deployed service members have not been examined, but excessive heat, weight of body armor, and environmental stress are plausible contributing elements.

*Factors Contributing to Cardiovascular Risk*

Age and Gender

It is well known that CVD risk increases with age, and while 68% of enlisted personnel are under the age of 30, 27% of commissioned officers and 31% of warrant

officers are over 40.[17] The reserve population is even older: the average age of reserve officers is 42 years, while the average age of enlisted personnel is 31 years.[18]

Males carry a greater CV risk than females in younger age groups.[19] Men comprise between 79-94% of the active military force, depending on branch of service,[4] so by virtue of gender composition, much of the military force is at greater risk than if the gender distribution was equal.

Hypertension and Dyslipidemia

Hypertension and dyslipidemia are major CV risk factors and are found even in the normal weight population.[20] The importance of hypertension and dyslipidemia in the development of CVD is captured in both the FRS [19] and the Adult Treatment Panel III (ATP III) guidelines.[21] At age 50, the lifetime risk for CVD in a normotensive versus hypertensive (greater than or equal to 140/90 mmHg) individual is 26.6% and 46.4%, respectively. Total cholesterol also plays a role in lifetime CVD development with a risk of 26.2% in subjects with cholesterol less than 180 mg/dl and 45.3% in subjects with cholesterol equal or greater than 240 mg/dl.[22] Such findings underscore the importance of CV risk modification early in life.

While the focus of CV risk targets low density lipoprotein cholesterol (LDL-C), the significance of high density lipoprotein cholesterol (HDL-C), very low density lipoprotein cholesterol (VLDL-C), and non-HDL-C and their relationship with the development of atherosclerosis and CVD is evident. In pooled Framingham data, VLDL-C predicted acute coronary events independently, and non-HDL-C predicted coronary events better than LDL-C. [23] Non-HDL-C significantly predicted the presence of post-mortem cardiac lesions

in men and women between the ages of 30 and 34 years.[8]

Both the ATP III [21] and the FRS[19] incorporate the negative impact of a low HDL-C and the protective effects of an elevated HDL-C in calculating risk. Researchers with the Veterans Affairs High-Density Lipoprotein Intervention Trial study clearly demonstrate that elevation of HDL-C and reduction of triglycerides through the use of gemfibrozil resulted in a 22% relative risk reduction of major cardiac events.[24] This study included only men, but the Air Force/Texas Coronary Atherosclerosis Prevention Study included both genders; after treatment with lovastatin, significant reductions in LDL-C and triglycerides and significant improvement of HDL-C similarly resulted in a 37% risk reduction of coronary artery events.[25]

Hypertension, dyslipidemia, or both are prevalent in active duty service members. In the 2005 Department of Defense survey assessing the health related behaviors of over 16,000 active duty personnel, 12.1% of respondents had previously been advised of their elevated blood pressure[4] and in the 2002 survey of over 12,000 service members, 17.7% were advised of abnormal lipoprotein metabolism.[26] These frequencies are based on self report, however, and may not reflect true prevalence of these conditions. Furthermore, these surveys include service members of all ages, and inclusion of the youngest service members in these rates may not reflect accurately the prevalence in those above the age of 30 who are likely to be at higher risk. The prevalence of multiple risk factors is not reported; such data are useful as an individual's CV risk rises with greater numbers of risk factors.[27]

Recent descriptive studies of military personnel in which risk factors are actually

measured rather than identified through self report indicate higher rates of hypertension and dyslipidemia.[28, 29] Impressive rates of CV risk factors were identified in active duty personnel between 40 and 45 years (N=999): hypertension in 29.5%, hypertriglyceridemia in 24.4%, and low HDL-C in 20.3%.[29] Some support is also provided by a small convenience sample of 58 active duty personnel where hypertension was detected in 38%, elevated triglycerides in 28%, and low HDL-C in 31% of the sample.[28]

Smoking

Evidence exists unequivocally supporting smoking as a significant risk factor for CVD. One illustration of this effect is among a young group of 77 subjects who had completely normal angiography but had experienced an AMI. Researchers found that smoking status was the only risk factor documented in 69% of subjects; the average age was 42 $\pm$ 8.3 years and 43% were less than 40 years of age.[30] Risk factor assessment, however, did not include assessment of family history of premature CAD.

While tobacco use in the military has declined significantly in the last 25 years, there has been a recent rise in smoking rates despite its associated morbidity. The overall rate of smoking in all services is 32.2%,[4] with the Army and Marine Corps showing the highest rates at 38.2% and 36.3%, respectively. Smoking rates increase with deployments to Iraq[31, 32] which likely contributes to the incidence of AMIs in individuals who by all accounts should be healthy.

Overweight and Obesity

Classification of overweight and obesity is based on BMI and estimates the degree of an individual's body fat. Indeed, cardiovascular disease is associated with overweight

and obesity [3] and mortality from CVD increases with BMI.[33] Over 65% of the adult population 20 years and older in the U.S. meet the criteria for being overweight (BMI $\geq$ 25) or obese, with 30.4% of American adults characterized as obese (BMI $\geq$ 30).[34] There are no barriers to this epidemic: trends in increased weight across ethnic groups and gender have been noted since the 1960s. [3] The U.S. military population is showing similar trends; over 60% of service members have a BMI $\geq$ 25;[4] however, overweight or obesity prevalence in the military may be inflated because of the high proportion of muscular, physically conditioned individuals.[35]

Glucose abnormalities

The ATP III guidelines [21] identify diabetes as a CAD risk equivalent when computing an individual's FRS. Researchers assessed lifetime risk of CVD and determined that of all cardiac risk factors, people with diabetes at age 50 had the highest risk of CVD development, occurring in 67.1% of men and 57.3% of women.[22] Furthermore, males with diabetes had lower rates of survival when compared to males without diabetes.

Studies on diabetes and other glucose abnormalities are uncommon among military service members, likely due to the infrequent presentation of these conditions in a relatively young population, but also because individuals with diabetes are generally restricted from entering the service. In a convenience sample of healthy soldiers (N=625), 3.2% of the participants had abnormal carbohydrate metabolism.[36] Researchers in other studies show elevations of fasting glucose in 3%[29] to 7%[28]of healthy service members. Military service members diagnosed with diabetes are more

likely to be enlisted, non-white, and have a greater BMI than those without diabetes, not unlike risk factors for those seen in civilian studies.[37]

Insulin Resistance

Evidence exists that insulin resistance increases the risk of CVD. [38] Insulin resistance is a physiologic process predisposing persons to dyslipidemia, glucose intolerance, endothelial dysfunction, hemodynamic changes, abnormalities in uric acid metabolism, elevated procoagulation and the presence of inflammatory markers.[39] A prospective study by Facchini and colleagues[40] demonstrated a greater prevalence of new onset hypertension and CVD in the most insulin resistant subjects when compared to those who are insulin sensitive, findings similar to those seen in larger studies.[41, 42] Insulin resistance is significantly correlated with BMI ($r = 0.54$)[43] and physical fitness ($r = -0.58$),[44] although McLaughlin and colleagues [43] found insulin resistance in 16% of subjects with a BMI <25 and insulin sensitivity in 36% of subjects with a BMI >30.

There is little information on insulin resistance in the U.S. military. Evidence exists, however, supporting significant elevations of fasting insulin levels in active duty service members with the metabolic syndrome when compared to those without the metabolic syndrome.[29] Fasting insulin level is only a surrogate measure of insulin resistance, however, and no studies on direct measurements were found in military populations.

Stress and Coronary Artery Disease

Though there is a known association of psychological stress and ACS, the precise mechanisms behind the relationship remain unclear.[45] When exposed to acute stress stimuli, a number of physiologic mechanisms are activated, possibly predisposing an

individual to an AMI. Stressors are known to have acute increases in blood pressure [46] and heart rate,[47] delayed recovery of systolic blood pressure, and increased platelet aggregate response.[48] Exposure to stress is also associated with changes in endothelial function,[49] presence of cardiac ischemia,[47] and increases in cardiac arrhythmias.[50]

Life stressors and Personality Traits

The literature is conflicting regarding life stress and its relationship with ACS. Ambulatory electrocardiograph monitoring captured myocardial ischemia during episodes of tension and frustration in a case-crossover study in patients with known CAD.[51] Moore and colleagues [52] found no relationship between angina pectoris, MI, or MI-death and occupation, lifestyle, or life stressors after controlling for traditional CV risk factors. In this 10 year prospective study, however, stress was measured only once at baseline and the measures may not have reflected accurately the level of stress experienced during the entire course of the study. Using similar methodology, however, participants in the Copenhagen City Heart Study with higher levels of stress had significantly greater risk of angina pectoris, but not MI.[53] No data on life stressors associated with CVD in U.S. military personnel could be found.

Hostility is emerging as a risk factor for CVD. After multivariable adjustment, participants in the Coronary Artery Risk Development in Young Adults Study had evidence of coronary artery calcifications with greater scores on the Cook-Medley hostility scale.[54] Indeed, hostile behavior in military personnel is seen after both combat duty[55] and military peacekeeping missions.[56] Researchers conducted a case-control study involving 49 asymptomatic U.S. Air Force flight personnel, examining personality

traits and manifestation of CVD. Investigators found that total cholesterol, blood pressure, and age were not significantly related to abnormal coronary angiography; rather, among non-smokers, subjects with higher scores on the Hostile Behavior Index had a greater prevalence of vessel disease than subjects with lower scores.[57]

War stressors

War related stressors are associated with both acute cardiac events and cardiac risk factors. During the Persian Gulf War, an increase in the number of AMIs was documented in Israeli civilians who were in close proximity to scud missile attacks from Iraq. The number of cardiac events during the attacks was greater from those seen the week prior to the war or at the same time in the previous year.[58]

Researchers designed a case-control study involving Lebanese civilians and demonstrated greater proportions of wartime stress exposures among CAD cases when compared to age and gender matched controls.[59] Additionally, subjects were twice as likely to have CAD when exposed to 2 or more stressors when compared to those exposed to less than 2 war stressors. Investigators assessed acute and chronic stressors, including kidnapping, injury, death, dissatisfaction with accommodations, and disruptions in utilities, all of which may be present in the current theaters of operation. These studies underscore the association of war-related stress and CAD, although findings may not be generalizable to the U.S. military population since they were conducted in older Israeli and Lebanese populations. However, young Croatian combat veterans (n=195, mean age 32 $\pm$ 4.6 years) with post traumatic stress disorder had both statistically and clinically significant elevations in their FRS, total cholesterol, LDL-C, and

triglyceride levels, and reductions in their HDL-C levels when compared to controls, even after controlling for BMI.[60] Both Army and Marine personnel are twice as likely to develop post traumatic stress disorder after a deployment to Iraq when compared to those who are not deployed [61] and today's service members can expect multiple or extended deployments.

Hazardous combat duty is highly stressful, and it is plausible that the Global War on Terror introduces a unique environment which predisposes vulnerable military personnel to ACS. In the first 18 days of the Iraq war, cardiac diagnoses accounted for 7.8% of the non-combat related medical evacuations to Germany; impressively, 7 of 9 non-combat related admissions to the intensive care unit were cardiac related [9], supporting a possible link ACS and acute stress. Between October 2001 and May 2006, cardiac disease accounted for most medical diagnoses requiring critical care transports from Iraq and Afghanistan to Germany (n=275). The average age of this group was 45 $\pm$ 10 years; 67% were military members (personal communication, Elizabeth Bridges, PhD August 3, 2007)

## Conclusion

There are significant gaps in the literature on CV risk assessment in military personnel, especially those deploying to a combat environment. Future research must be directed at assessment of CV risk factors in deployed service members and identification of any relationships between combat stress and CV risk profile or acute CV events.

Cardiovascular risk factors have potentially devastating consequences on the

combat readiness of the military. The military is often viewed as a young, fit population, but as the force ages, CV risk factors are increasingly evident. Consistent assessment and reinforcement of CV risk screening, and CV risk reduction activities must begin at the point of entry into the service in both the active duty and reserve population and continue throughout an individual's military career. Preventing an acute CV event in a vulnerable individual is particularly important during this time of increased operational requirements, allowing military personnel to remain physically fit and combat ready.

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## Chapter 3

### Introduction

Coronary heart disease continues to be the leading cause of mortality in men and women in the United States with a death occurring every minute from a cardiac event (Thom et al., 2006). Atherosclerotic lesions predispose individuals to a cardiovascular (CV) event most often through rupture of a plaque, precipitating a cascade of events leading to thrombosis and occlusion of a coronary artery. One of the worrisome features of atherosclerotic disease is that it is often asymptomatic, especially in young people; both early and advanced coronary atherosclerotic lesions are present in asymptomatic adults at autopsy (Enos, Holmes, & Beyer, 1953; McMahan et al., 2005; McNamara, Molot, Stremple, & Cutting, 1971). Artery lesions are influenced at an early age, with fatty streaks, the precursors to advanced lesions, found in children as young as 2 years of age and significant trends of fibrous plaque lesions increasing between the ages of 2-15 years (8%) to 26-39 years (69%) (Berenson et al., 1998).

The focus of this chapter is the physiologic processes related to CV disease (CVD), specifically, atherosclerosis and insulin resistance. The chapter concludes with an overview of physiologic responses to stress and their relationship to CV risk.

### Background

The atherosclerotic process starts at the endothelial cells that line the intima of the artery wall. In 1995, the American Heart Association classified the progression of atherosclerotic lesions into numerical categories, Type I through Type VI (Stary et al., 1995). In response to criticisms about the classification scheme (Virmani, Kolodgie, Burke, Farb, & Schwartz, 2000), the lead author of the original American Heart

Association classification suggested a modified scheme (Stary, 2000). The modified version is depicted in Figure 1. Though graded classification of lesions is used infrequently in recent literature, it is included in this chapter because the detailed description of the development and progression of atherosclerotic plaques that follow in this chapter corresponds with the nomenclature of the lesions.

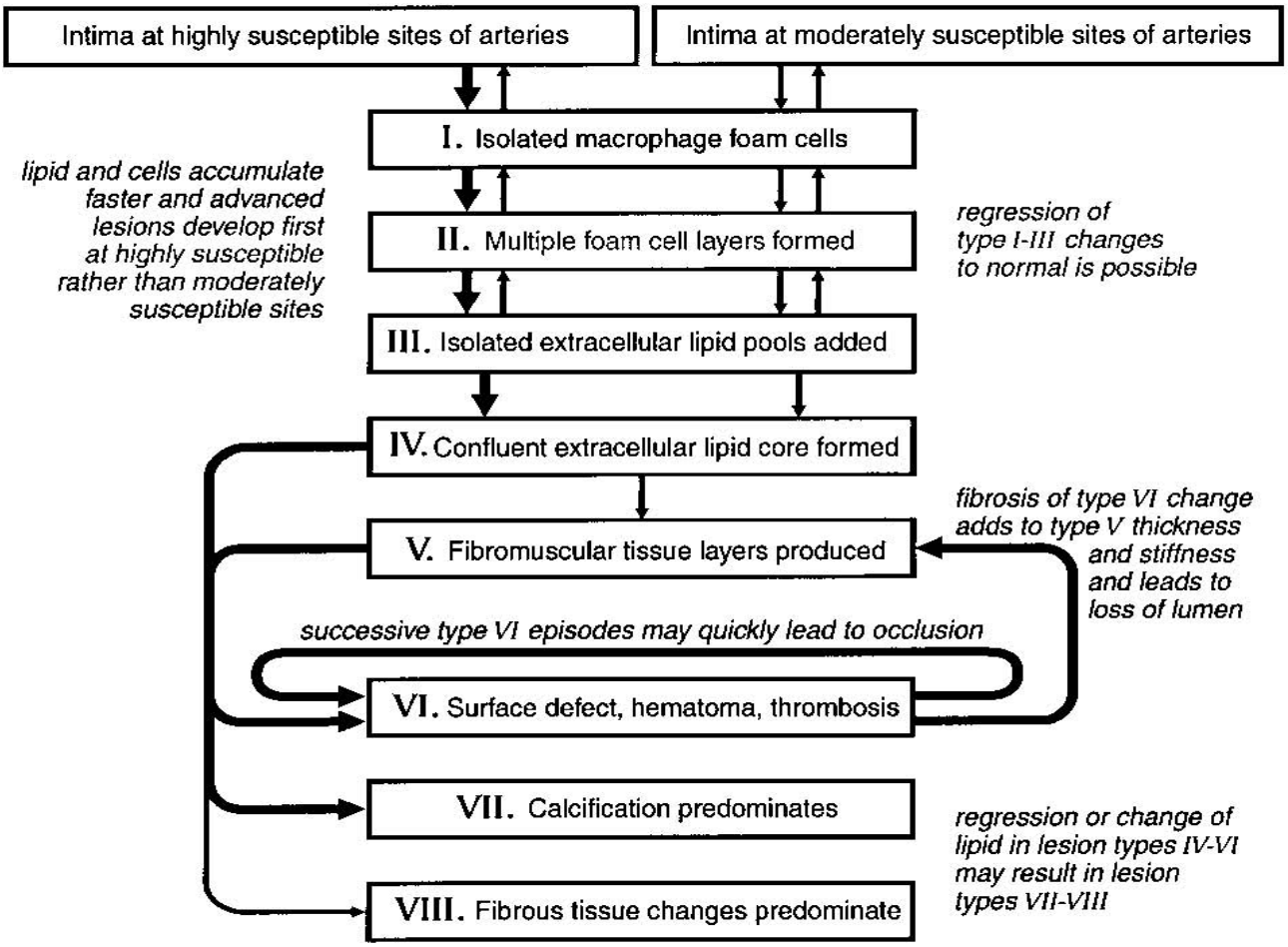



**Figure 1 Suggested classification of atherosclerotic lesions (Stary, 2000) (with permission)**

While classification of lesions may be useful for lesion histology analysis, emphasis rests with identifying patients at risk for a CV event. The concept of the "vulnerable patient" identifies patients with CV risk through characteristics of "vulnerable blood",

"vulnerable myocardium", and "vulnerable plaque" (Naghavi et al., 2003). Coagulability, arrhythmias, and plaque rupture are addressed throughout the chapter.

## Pathophysiology of Atherosclerosis

Historically, the focus of atherosclerotic lesions was the presence of hypercholesterolemia with subsequent plaque development. While lipid levels remain important, great focus is on the inflammatory processes that play an integral role in the evolution of an atherosclerotic plaque. Libby and Ridker (2006) separate lesion formation into three distinct phases*: initiation of the lesion, lesion progression,* and *complication.*

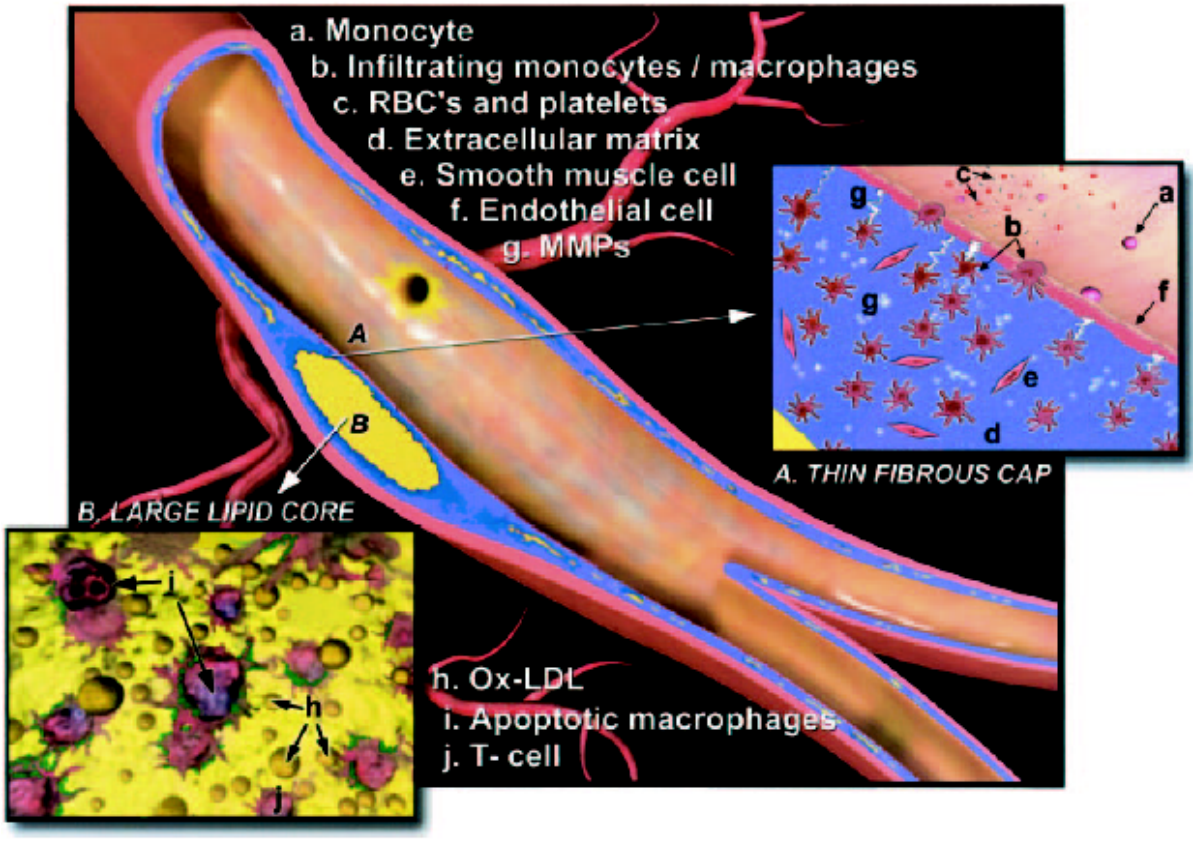
### *The Normal Artery*

The physiologic roles of the endothelium include selective permeability as well as regulation of vascular tone, vascular remodeling, inflammation, and thrombosis (Lusis, 2000). The artery wall is composed of three major layers bound by a layer of endothelial cells in closest proximity to the lumen. The intima is the innermost layer and is primarily made of connective tissue. The middle layer is the media, composed of smooth muscle cells. Finally, connective tissue with fibroblasts and smooth muscle cells are the components of the outermost layer, the adventitia (Lusis, 2000). The endothelium vasodilates or vasoconstricts in response to endogenous signals in the blood (Harris & Matthews, 2004). Nitric oxide is the most common vasodilator released by endothelial cells; the greater the response to nitric oxide, the better an individual's endothelial function. Nitric oxide also inhibits platelet aggregation and activation along the endothelium (Harris & Matthews, 2004). Endothelial cells release vasoconstrictors

in response to norepinephrine, hypoxia, and thrombin; tissue plasminogen activator, essential for fibrinolysis, is also released by endothelial cells.

*Initiation*

Inflammation is implicated in the formation of an atherosclerotic lesion. Inflammatory processes are stimulated by oxidized low density lipoprotein (LDL), resulting in the expression of adhesion molecules (Libby & Ridker, 2006), including intracellular adhesion molecule-1, vascular cell adhesion molecule-1, E-selectin and P-selectin by the endothelial cells (Fan & Watanabe, 2003). Adhesion molecules draw circulating monocytes to the endothelial surface; hyperinsulinemic and hypertensive states promote monocyte adherence to the endothelium (Chen et al., 1999). Cytokines, including interleukin-1, tumor necrosis factor-alpha, and monocyte chemoattractant protein, aid migration of monocytes through the endothelial cells into the intima layer of the artery (Fan & Watanabe, 2003). Monocytes move only in one direction; oxidized LDL prevent them from migration out of the intima (Diaz, Frei, Vita, & Keaney, 1997; Fan & Watanabe, 2003). The monocytes eventually differentiate into macrophages and further contribute to the inflammatory process through the release of pro-inflammatory cytokines and reactive oxygen species. They also absorb oxidized LDL and undergo modifications to become foam cells (Libby & Ridker, 2006). The development of an atherosclerotic lesion is illustrated in Figure 2.




RBC=red blood cell; MMP=matrix metalloproteinase degrades the extracellular matrix and weakens the fibrous cap; ox-LDL=oxidized LDL

**Figure 2 Mechanisms of atherosclerosis in a vulnerable plaque (Naghavi et al., 2003) (with permission).**

Patterns of blood flow affect the predilection of initial lesion development. Endothelial cells are elliptical and form tight junctions in the arterial walls. In arteries that curve or bifurcate, disruption of the blood flow occurs, resulting in shear stress, causing the endothelial cells to lose their elliptical shape and tight configuration. The disruption of cell junctions ultimately increases permeability of the endothelium, creating a prime selection site for LDL to infiltrate and start the inflammatory process associated with atherosclerosis (Lusis, 2000).

High-density lipoprotein (HDL) plays an integral role in prevention of plaque formation through reverse cholesterol transport whereby HDL transports lipid filled macrophages out of the intima (Libby & Ridker, 2006). Other anti-atherogenic mechanisms of HDL cholesterol are not entirely understood. Anti-inflammatory effects are associated with paraoxonase-1, an antioxidant enzyme that is a linked to HDL and is negatively correlated with oxidized LDL (r=-0.856) (Mastorikou, Mackness, & Mackness, 2006). Based on large prospective studies, high levels of HDL cholesterol are recommended, however, HDL may have pro-inflammatory effects (Roberts, Ng, Hama, Eliseo, & Barnard, 2006). In contrast, evidence supports reconstituted HDL reduces the expression of vascular cell adhesion molecule *in vitro* (Clay et al., 2001) and reduces reactive oxygen species *in vivo* (Nicholls et al., 2005). Rather than focusing on the value of HDL cholesterol, HDL function may have greater predictive value in CVD (Navab et al., 2005).

*Progression*

This phase is characterized by the transition from fatty streaks to a fibrofatty lesion, including the formation of a fibrous cap over an atherosclerotic plaque (Libby & Ridker, 2006). In response to inflammation, chemoattractants also stimulate the movement of smooth muscle cells from the media to the intima. The smooth muscle cells multiply and produce substances that contribute to the fibrotic nature of the lesion. Necrotic foam cells, lipids, and cell debris are underneath the fibrous cap and add to the lipid core. T-lymphocytes are also found in atherosclerotic lesions and affect plaque progression in the intima (Fan & Watanabe, 2003). Though atherosclerotic

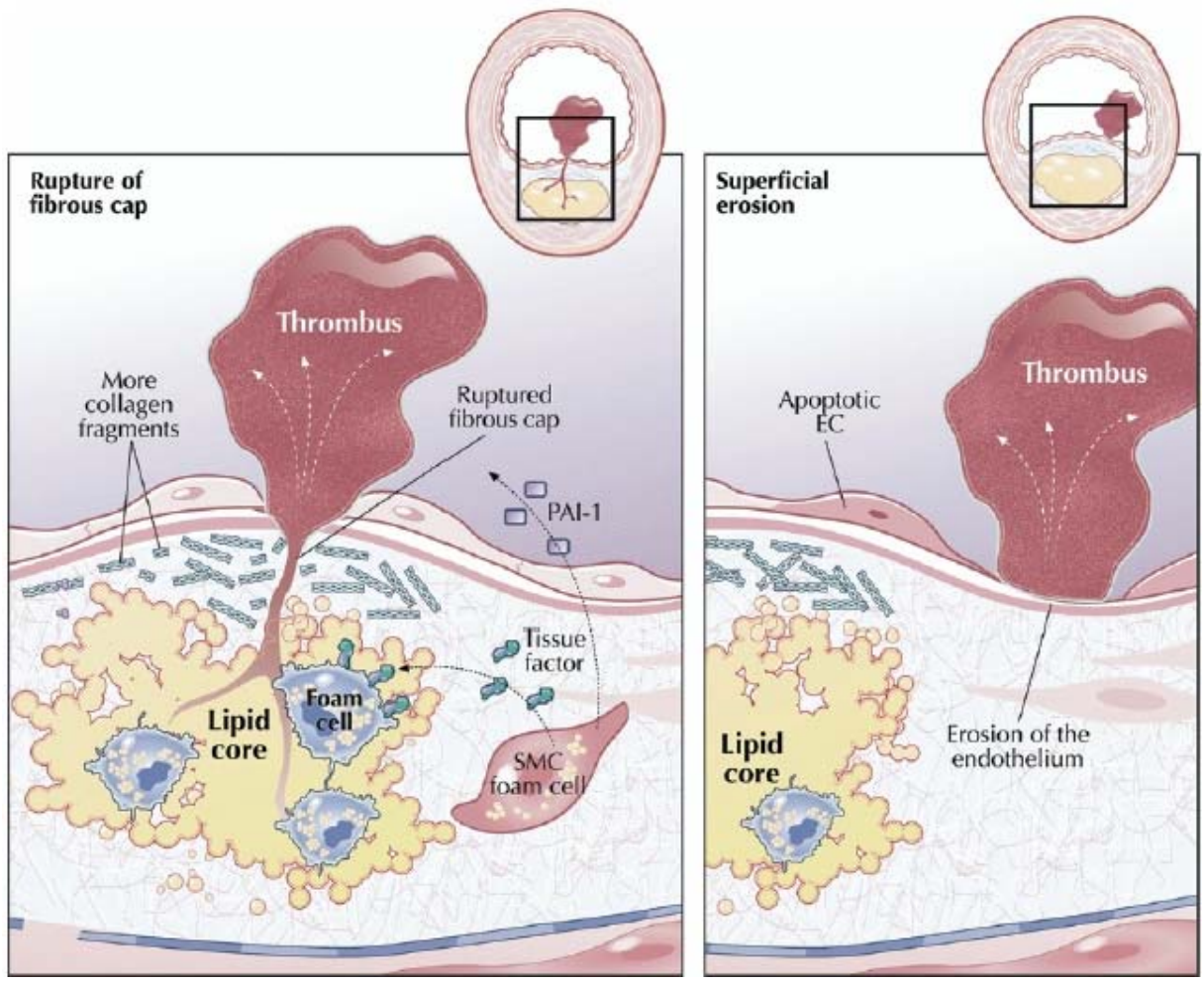
lesions typically grow toward the adventitia, a point is reached when they begin to grown inward toward the lumen of the artery (Lusis, 2000). The lumen remodels, however, limiting artery stenosis (Libby & Ridker, 2006; Viles-Gonzalez, Fuster, & Badimon, 2006).

As monocytes, LDL, smooth muscle cells, and other cellular material infiltrate the innermost layer of the intima, the area becomes thickened (Viles-Gonzalez, Fuster, & Badimon, 2006). Ultrasound evaluation of intima-media thickness is a surrogate marker for atherosclerosis in a number of studies and greater thickness is associated with increased CV risk as measured by the Framingham risk score (Stamatelopoulos et al., 2006; Touboul, Labreuche, Vicaut, & Amarenco, 2005).

*Complication*

The complications of an atherosclerotic lesion include plaque rupture and erosion of endothelial cells, depicted in Figure 3. Researchers acknowledge that artery stenosis occurs as a complication, but to a much lesser degree than once thought (Libby & Ridker, 2006).

*Plaque Rupture* It is important to note that widespread vessel disease is not necessary to manifest complications of atherosclerotic disease; rather, plaque rupture at the site of a single lesion is sufficient to cause sudden cardiac death (Berenson et al., 1998). The thickness of the fibrous cap is an important factor in determining the stability of the lesion. With a large lipid core and a thin fibrous cap, the “shoulder” area, or base of the




EC=endothelial cells; SMC=smooth muscle cell; PAI-1=plasminogen activator inhibitor

**Figure 3 Complications of the atherosclerotic plaque (Libby & Ridker, 2006) (with permission)**

plaque has greater potential to rupture when compared to plaques with a thick fibrous cap (Fan & Watanabe, 2003). Apoptotic cells accumulate around the lipid core, drawing in additional inflammatory cells (Viles-Gonzalez, Fuster, & Badimon, 2006). Large numbers of inflammatory cells in the "vulnerable plaque" contribute to the degradation of the fibrous cap (Lusis, 2000). The matrix metalloproteinases produced by macrophages weaken the cap sufficiently to the point of rupture (Fan & Watanabe, 2003). When a plaque ruptures, the contents of the lipid core precipitate thrombosis and subsequent ACS from occlusion of the artery lumen (Fuster, Badimon, Badimon, &

Chesebro, 1992a). The presence of plasminogen activator inhibitor-1 in inflammatory states, exacerbates the thrombotic process through inhibition of the fibrinolytic pathway (Libby & Ridker, 2006).

*Endothelial Cell Erosion* Approximately one-third of ACS result from endothelial cell erosion (Viles-Gonzalez, Fuster, & Badimon, 2006). Wearing of the endothelium stimulates events contributing to thrombus formation, either through desquamation of the cells or apoptosis of the cells (Libby & Ridker, 2006). After injury to the endothelium, platelets and fibrin congregate on the arterial wall. The endothelium releases urokinase and plasminogen activator that, in normal circumstances, lead to the lysis of the fibrin; however, as with plaque rupture, plasminogen activator inhibitor disrupts the fibrinolytic pathway, and dissolution of the thrombus does not occur (Castelli, 1996). While the injury to the endothelium is an important factor, so is a person's propensity for thrombosis development, referring to the concepts of "vulnerable plaque" and "vulnerable blood" combining and giving rise to the high risk, or "vulnerable patient" (Naghavi et al., 2003). Conditions that enhance a person's thrombogenicity include smoking, elevated LDL cholesterol (Viles-Gonzalez, Fuster, & Badimon, 2006), hyperglycemia and insulin resistance (Stegenga et al., 2006).

*Artery Stenosis* Evolution of research on ACS reveal that the contents of atherosclerotic plaques are more important than simply lumen narrowing (Corti, Hutter, Badimon, & Fuster, 2004; Fuster, Badimon, Badimon, & Chesebro, 1992a; Lusis, 2000). Plaque rupture accounts for approximately 70% of "culprit" lesions responsible for cardiac death. Of these, only 20% are associated with stenotic vessels (Naghavi et al., 2003).

Lesions that tend to cause greater narrowing of the lumen include those with a smaller lipid core because they usually have a thicker fibrous cap. Furthermore, the thickness provides greater stability for the lesion and plaques with these characteristics are less likely to rupture (Fan & Watanabe, 2003).

## Pathophysiology of Insulin Resistance and Cardiovascular Disease

For insulin sensitive individuals, insulin stimulates glucose uptake in adipose tissue and skeletal muscle, promotes hepatic glycogen storage, inhibits hepatic glucose release, and suppresses lipolysis with subsequent release of free fatty acids into the circulation. Insulin stimulated glucose uptake into specific tissues allows individuals to maintain glucose homeostasis. When the body becomes insensitive to insulin, abnormalities in normal physiologic functions occur. Resistance to insulin may not equally affect all tissues; indeed, abnormalities may be present in adipose tissue while insulin mediated glucose uptake in the skeletal muscle remains normal (Reaven, Lithell, & Landsberg, 1996).

Insulin resistance is a risk factor for CVD (Reaven, 1988; Robins et al., 2003; Rutter, Meigs, Sullivan, D'Agostino, & Wilson, 2005), and while often thought of as a physiologic process associated only with obesity, insulin resistance is found in normal weight, overweight and obese individuals (McLaughlin, Allison, Abbasi, Lamendola, & Reaven, 2004). Though there are a number of clinical manifestations that cluster in the presence of insulin resistance, the focus in this chapter is on physiology of hyperglycemia, dyslipidemia, hypertension, and endothelial dysfunction.

*Hyperglycemia*

The pancreas of an insulin resistant individual secretes greater amounts of insulin to preserve glucose homeostasis; however, despite maintenance of euglycemia, untoward CV risks may develop due to hyperinsulinemia (Reaven, 1988). Despres and colleagues (1996) found hyperinsulinemia independently predicts cardiac events (N=196): men with hyperinsulinemia had more than one and one half times the odds of an ischemic cardiac event when compared to healthy controls (adjusted OR 1.6, 95% CI 1.1-2.3).

Though the increased insulin secretion initially prevents hyperglycemia, such a response cannot continue, and eventually insulin levels return to normal and insulin resistant individuals develop overt hyperglycemia. Elevated glucose levels are thought to occur not only by the loss of the pancreas' ability to compensate for the insulin resistance, but also when the adipose tissue becomes insulin resistant and the insulin no longer suppresses lipolysis of triglycerides in the adipocytes. When lipolysis occurs, free fatty acids are released. Free fatty acids suppress glucose uptake and promote glucose production in the liver (Reaven, 1988), though the role of latter response in the presence of hyperglycemia is not as great as once thought (Reaven, 1995a). The hepatic responses to free fatty acids compound the clinical finding of hyperglycemia in the insulin resistant individual.

*Dyslipidemia*

One of the metabolic consequences of insulin resistance is abnormal lipoprotein metabolism and the associated atherogenic lipid profile of hypertriglyceridemia, low

HDL cholesterol, small, dense LDL particles and post-prandial lipemia (Reaven, 1988).

Failure of the insulin to suppress lipolysis triggers another clinical finding of insulin resistance: the elevation of circulating free fatty acids result in increased production of triglycerides in the liver. Fatty acids and triglycerides are moderately correlated (r=.46) (Pirro et al., 2002), and a dose response relationship exists between insulin levels and triglyceride production: the more hyperinsulinemic an individual, the greater the triglyceride production, a function of the combination of increased levels of free fatty acids and insulin levels (Reaven, 1995a). Increased hepatic triglyceride synthesis leads to an increased production and secretion of triglyceride-rich VLDL.

In addition to elevated triglycerides leading to greater VLDL production, there is a well-documented relationship between hypertriglyceridemia and low HDL cholesterol; measures of insulin resistance have moderate to high correlations with triglycerides (r=0.57) and HDL cholesterol (r=-0.40) (McLaughlin et al., 2005). In the presence of increased VLDL, two important processes occur that lead to the atherogenic lipid profile associated with insulin resistance. First, cholesteryl ester transfer protein (CETP) mediates the transfer of cholesteryl ester from HDL to VLDL in exchange for a triglyceride molecule. The triglyceride-rich HDL is hydrolyzed by hepatic lipase, forming small, dense HDL particles that are readily catabolized (Adiels, Olofsson, Taskinen, & Boren, 2008). Second, CETP also mediates the transfer of cholesteryl ester from LDL to VLDL with VLDL relinquishing a triglyceride molecule, similar to the process that occurs with HDL. Enzymatic lipases hydrolyze the triglyceride-rich LDL, resulting in the formation of small, dense LDL particles that have a decreased affinity for LDL receptors,

and enjoy an extended stay in the circulation. Findings are conflicting regarding the possibility that increases in CETP mass account for increases in small, dense LDL particles (Sandhofer et al., 2006; Watson et al., 1994). It is well established, however, that small, dense LDL particles are more prone to oxidation and are associated with increased CV risk. Evidence supports both small, dense LDL cholesterol in the presence of hyperinsulinemia (Lemieux et al., 2001; Reaven, Chen, Jeppesen, Maheux, & Krauss, 1993), and a strong negative correlation (r=-0.77) between triglyceride/HDL cholesterol ratio and LDL particle diameter (McLaughlin et al., 2005).

*Hypertension*

Individuals who are most insulin resistant are more likely to develop hypertension (Facchini, Hua, Abbasi, & Reaven, 2001), and have higher blood pressures than those who are insulin sensitive (Haffner, Mykkanen, Festa, Burke, & Stern, 2000; McLaughlin, Allison, Abbasi, Lamendola, & Reaven, 2004; Zavaroni et al., 2000). The mechanisms behind the relationship between hypertension and insulin resistance are not clear; not all who have hypertension are insulin resistant; similarly, not all individuals with insulin resistance have hypertension (Reaven, Lithell, & Landsberg, 1996). Approximately one half of individuals with hypertension are insulin resistant (Reaven, 1995b), but a causal relationship has not been identified. Evidence exists that insulin resistance increases sympathetic nervous system activity, explaining increases in blood pressure (Facchini, Stoohs, & Reaven, 1996). Another mechanism that may be involved is insulin-stimulated increases in sodium reabsorption (Reaven, 1988).

*Endothelial Dysfunction*

Endothelial dysfunction occurs when an individual's vasculature inappropriately or inadequately vasodilates or vasoconstricts to stimuli. Additionally, vessels with endothelial dysfunction promote cell adhesion, coagulation, inflammation, and permeability to atherogenic lipoproteins, thereby contributing to an individual's CV risk (Cersosimo & DeFronzo, 2006). Not surprisingly, damage to the endothelium can be measured with biomarkers implicated in the atherosclerotic process, including intercellular and vascular cell adhesion molecules, tumor necrosis factor alpha, C-reactive protein, and interleukin-6. There is a known relationship between insulin resistance and endothelial dysfunction. Nitric oxide is an endogenous vasodilator, and asymmetric dimethylarginine, a nitric oxide synthase activity inhibitor, is highly correlated (r=0.73) with steady state plasma glucose, a measurement of insulin resistance (Stuhlinger et al., 2002).

## Pathophysiologic Changes Related to Stress

*"My life is in the hand of any rascal who chooses to put me in a passion"*
*Sir John Hunter (1728-1793)*

*Acute Stress Responses*

Acute stress stimuli activate the sympathetic nervous system (SNS) and the cascade of physiologic events that follow potentially place a susceptible individual at greater risk for a CV event. Stimulation of the SNS results in catecholamine (norepinephrine, epinephrine) release and enhances platelet activity and greater levels of fibrinogen (Viles-Gonzalez, Fuster, & Badimon, 2006), factors that promote the thrombogenicity of an individual. Proinflammatory biomarkers also increase with

induced mental stress (Hamer & Steptoe, 2007).

Another system activated in response to stressors is the hypothalamic-pituitary-adrenal axis (HPA axis). The hypothalamus releases corticotrophin-releasing hormone, stimulating the release of adrenocorticotropin-releasing hormone from the pituitary gland, and cortisol is released from the adrenal cortex. While the SNS is activated immediately upon exposure to a stressor, HPA axis activation occurs minutes to hours afterward (King & Hegadoren, 2002). While in the short term, glucocorticoids and catecholamines enhance adaptation to stressors, dysregulation of their response or secretion to stressors can result in deleterious health effects (McEwen, 2001).

Though there is an association of psychological stress and ACS, the precise mechanisms behind the relationship remain unclear (Thrall, Lane, Carroll, & Lip, 2007). In contrast to simply evaluating the traditional CV risk factors of hypertension, dyslipidemia, glucose abnormalities and smoking, Rozanski and colleagues (1999) conceptualize a framework illustrating the physiologic effects of stress and clinical consequences which may increase the risk of a CV event in an individual (Figure 4). The physiologic effects that are potentially implicated in an acute CV event are described individually in the pages that follow. Many studies reviewed include simulated mental stressors, such as arithmetic and speaking tasks. While useful, it is unlikely simulated tasks capture the magnitude of physiologic responses associated with actual or perceived stressors in an individual's life (Rozanski, Blumenthal, & Kaplan, 1999).

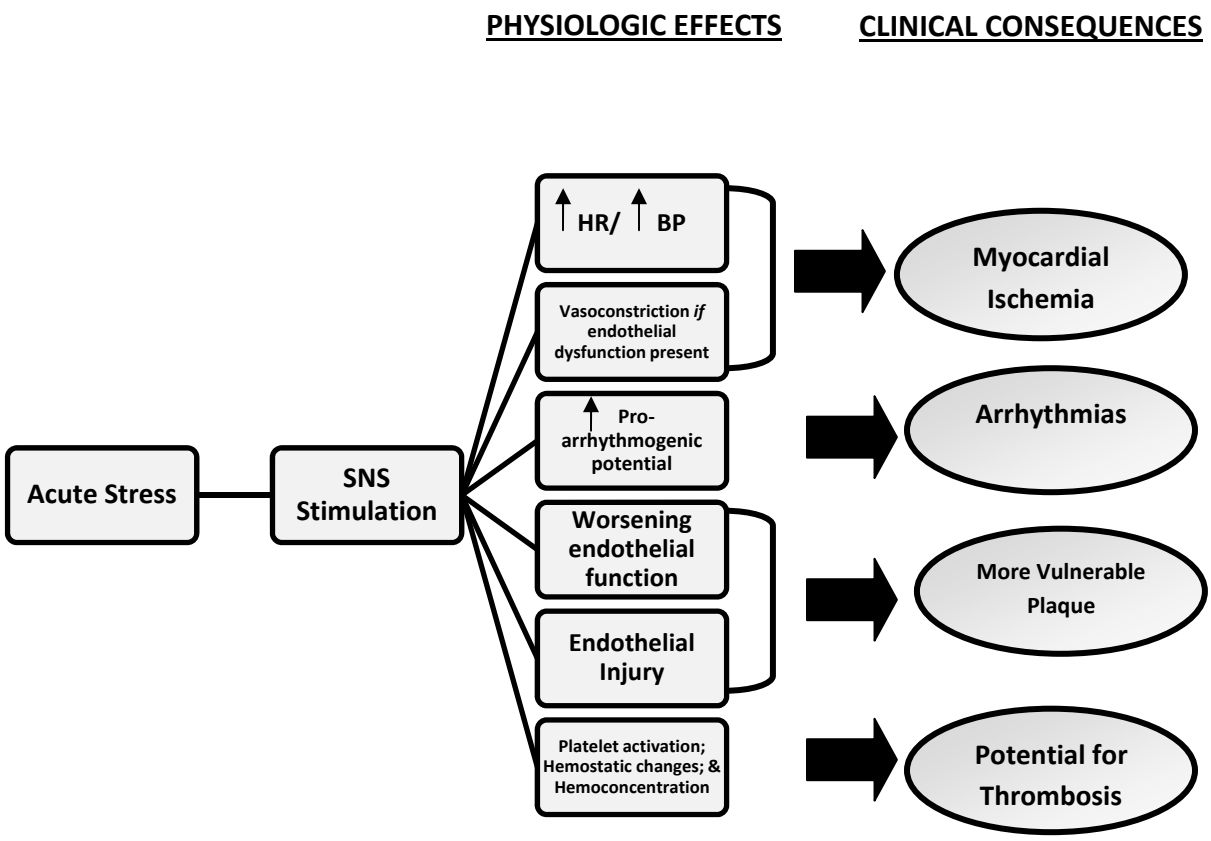



**Figure 4 Framework of acute stress and CVD (adapted from Rozanski, Blumenthal, & Kaplan, 1999) (with permission).**

*Vasomotor Responses: Blood Pressure and Heart Rate* In the presence of increased heart rate and transient elevations in blood pressure, a vulnerable plaque may be subject to fissuring or disruption (Fuster, Badimon, Badimon, & Chesebro, 1992b), increasing the possibility of ACS. Blood pressure is evaluated often in response to actual or perceived stress. In a natural experiment, investigators studied the influence of acute wartime stress (N=13) on Israeli civilian patients wearing ambulatory blood pressure

monitors at the start of Gulf War I (Weisenberg, Meisel, & David, 1996). Statistically and clinically significant relationships were identified only at the start of the war when patients were subjected to actual or perceived threat from missile attacks from Iraq when compared to their control measurement 3 months post-war. The relationship is somewhat limited by the fact that this is a very small sample and that some participants were treated with antihypertensive medications.

The workplace is an area of great interest to study the effects of job strain and its impact on CV risk factors. High levels of job stress are identified with differences in vasomotor responses when compared to similar groups with low job stress (Steptoe, Cropley, & Joekes, 1999). In a relatively young group (N=162, mean age 38.6 $\pm$ 2 years), significant overall increases were noted between baseline blood pressures and heart rate when performing simulated mental stress tests. Investigators also identified a significant increase in systolic blood pressure between teachers in low versus high job stress when completing an uncontrollable task, with a mean change of 13.4 mmHg in the high stress group, and 9.1 mmHg in the low stress group. While statistically significant, the clinical significance is unclear because only the mean baseline systolic blood pressure for the entire group is provided (116 mmHg), and the authors note no significant differences in baseline systolic blood pressure between groups. More interestingly, the high stress group had non-significant reductions in their systolic blood pressure, mean blood pressure, and in women, heart rate between daytime and evening hours, while the low stress group had significant reductions in these parameters. The findings were independent of BMI, age, gender, and baseline blood pressure, suggesting

the presence of persistent physiologic changes related to stress (Steptoe, Cropley, & Joekes, 1999). Consistent with these findings, investigators identified significant increases in systolic blood pressure, diastolic blood pressure and heart rate in a young healthy sample (N=40; mean age men 19.95 ± 1.15 years, women 21 ± 1.81 years) in response to simulated mental stressors, though none reached clinical significance (Veldhuijzen van Zanten et al., 2004).

There is evidence of greater elevations in blood pressure seen in subjects with a history of CAD (Ramachandruni et al., 2006; Yeung et al., 1991). In response to a simulated mental stressor, investigators elicited statistically significant and profound clinical differences from baseline measurements to peak measurements during the simulated stressor in systolic blood pressure (130.1 ± 13 mmHg to 190 ± 26mmHg), diastolic blood pressure (76.8 ± 5 mmHg to 103.2 ± 12 mmHg) and heart rate (64.3 ± 9 bpm to 86 ± 14 bpm) (Ramachandruni et al., 2006).

*Vasoconstriction and Endothelial Dysfunction* Endothelial dysfunction is a significant risk factor for the initiation of atherosclerotic plaques (Harris & Matthews, 2004). Elucidating the mechanisms behind stress related vasomotor responses is ongoing. Investigators studied mental stress testing in a small sample (N=23) of young healthy subjects, free of CVD to ascertain mechanisms behind changes in endothelial function. While significant constriction was seen in the flow-mediated diameter of the radial artery in response to simulated stress, after infusions of norepinephrine or an endothelin-A receptor antagonist, they found no changes in artery diameter, suggesting that activation of the endothelin-A receptors is responsible for stress induced flow

mediated diameter changes and not norepinephrine surges (Spieker et al., 2002). Indeed, increased levels of endothelin-1 are documented in young men undergoing behavioral and physical stressors (Treiber, Kapuku, Davis, Pollock, & Pollock, 2002).

Mental stress induced cardiac ischemia is associated with an increase in all cause mortality (Sheps et al., 2002). Cardiac ischemia resulting from mental stress may not manifest itself with chest pain or clinical findings seen on an electrocardiogram. To test "mental stress induced ischemia", investigators studied patients (N=21) with a documented history of cardiac disease, but with a negative exercise or chemical stress test. Additional perfusion studies revealed that 29% had apparent ischemic changes in response to mental stress; furthermore, subjects did not appreciate symptoms of ischemia, and the changes were not detectable on electrocardiogram (Ramachandruni et al., 2006). Findings from this study suggest there are differences in responses to physical stress versus psychological stress.

Subjects (N=30, mean age 57 $\pm$ 2 years) undergoing a diagnostic cardiac catheterization were subjected to either an experimental group undergoing a stressful verbal task (n=26) or a control group undergoing a non-stressful verbal task (n=4) (Yeung et al., 1991). Difference in response between groups in stenosed, irregular, and smooth coronary artery segments was found when exposed to mental stress. While the smooth arteries responded as expected by dilating 3 $\pm$ 3%, the stenosed and irregular segments constricted by 24 $\pm$ 4% and 9 $\pm$ 3%, respectively, with a subsequent decrement in myocardial perfusion. Such differences lend support for disruption of normal vasomotor responses in diseased arteries when exposed to stressors. Additional

evidence exists supporting the finding of vasoconstriction in diseased vessels in response to simulated stressors, however, the investigators also document similar and significant vasoconstriction of approximately 6% in coronary arteries of participants with and without CAD (Lacy et al., 1995). Differences between studies may be attributed to a dose-effect relationship with the latter study engaging the participant in greater stress burden.

*Arrhythmias* Indeed, the presence of arrhythmias in relationship to stressors is well documented. The percentage of ectopic ventricular beats increased during periods of emotional stress in participants wearing holter monitors (N=457, mean age 59 $\pm$ 14 years) (Culic, Silic, & Miric, 2005). In a small study (N=50), investigators found that when compared to when compared a control group of older individuals who experienced ACS (57.1 $\pm$ 8.1 years), young survivors of idiopathic ventricular fibrillation with subsequent cardiac arrest (mean age 36 $\pm$ 11.6 years) experienced greater chronic life stressors over the past 6 months and acute stressors 24 hours prior to the event. Controlling for age did not change the differences between groups on the Perceived Stress Scale (Lane et al., 2005). While no differences were noted between groups on smoking status, education level, household income, hostility, work stress and social support, a glaring omission in this study was failure to assess and control for other major CV risk factors.

*Platelet Activation/Hemoconcentration* Investigators studied two groups of men who experienced ACS after an emotional event and those who had no association of their AMI with an emotional event. After subjecting them to mental stress, platelet aggregation was significantly greater in the former group (Strike et al., 2006). In a meta-

analysis, Thrall and colleagues (2007) review the association of hemostatic responses to mental stress. While many of the studies document increases in several clotting factors, fibrinogen, D-dimer, and thrombin-antithrombin complex, no changes were noted in activated partial thromboplastin time and prothrombin time. Mixed findings are noted with respect to changes in tissue plasminogen activator. Enhanced platelet aggregation and increases in von Willebrand Factor have also been associated with mental stress. Greater perceived stress and greater cardiac hyperresponsivity is associated with increases in hematocrit and reduction of plasma volume (Veldhuijzen van Zanten et al., 2004). Hemoconcentration and platelet activation may also contribute to shear stress and subsequent thrombus formation.

*Chronic Stress Response*

Hans Selye introduced the concept of "general adaptation syndrome" in 1936 (Selye, 1936/1998). He described the three stages of physiologic responses in animal models when exposed to repeated stressors: "general alarm reaction", resistance, and exhaustion. Much of his work forms the cornerstone of subsequent work on the role of stress and biologic function.

Because individuals perceive stress differently, there are variable responses to stress. Most recently, the concept of allostasis and allostatic load are proposed to provide a conceptual framework for the relationship between chronic environmental and psychological stressors and adverse health (Kario, McEwen, & Pickering, 2003). Briefly, "allostasis" refers to an the inability to respond appropriately to a specific stressor through activation of the SNS and HPA axis through the release of

catecholamines and glucocorticoids. When the stressor is no longer a threat, the levels return to baseline. In individuals with persistent exposure to allostatic load, catecholamine and glucocorticoid dysregulation may occur, causing abnormal response patterns to stress. Proposed models include hyperresponsivity, prolonged recovery after stress exposure, inability to adapt to repeated stressors, and insufficient response to stressors. Abnormalities in biological measures are used to identify allostatic load.

*C-Reactive Protein* High sensitivity C-reactive protein (hsCRP) is a non-specific marker for inflammation, but in the presence of other CV risk factors, hsCRP may offer additional prognostic information. Ridker and colleagues (2004) cite large prospective studies identifying persons with multiple CV risk factors and hsCRP levels greater than 3 with higher risks of CV events. Investigators suggest that exposure to chronic stress may elevate hsCRP levels (Melamed, Shirom, Toker, Berliner, & Shapira, 2004), unfortunately, the findings are inconsistent. Prolonged fear of terror as measured by perceptions of personal safety, high tension in crowds, and terrorist attacks affecting family members predicted hsCRP levels in Israeli women only (N=431, mean age 48.3 $\pm$ 9.8 years), even after controlling for the multiple confounders affecting hsCRP values (Melamed, Shirom, Toker, Berliner, & Shapira, 2004). In a study of healthy university employees (N=43, mean age women 44.4 +/- 9.8, men 47.4 + 10.9), hsCRP had a moderate positive correlation with psychological stress (r= 0.37), perceived stress (r=0.39), and occupational strain (r=0.44) (Hapuarachchi, Chalmers, Winefield, & Blake-Mortimer, 2003). Additionally, significant differences in hsCRP in normal and high stress groups were identified, with no differences identified between gender. This study is

limited not only by its small size, but for failure to control for hsCRP confounders. Strict inclusion criteria, however, precluded participation of individuals on medications or if they had an abnormal complete blood count. In a different study, investigators found a significant association of hsCRP with chronic stressors, but this association was eliminated when researchers controlled for BMI, diabetes and psychosocial factors (Ranjit et al., 2007).

## Conclusion

Defining the physiologic processes leading to CVD has evolved dramatically, but questions remain on the mechanisms behind the relationship between stress and acute CV events. While several theories for potential mechanisms exist, and many studies support physiologic changes associated with stress, there is no causative link. Biomarkers are immensely helpful in quantifying and stratifying individuals into risk categories; however, more work is needed in this area to better define situational characteristics or personality traits that affect cardiac risk in the vulnerable patient.

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## Chapter 4

### Introduction

*"Both patients and physicians may ignore or not adequately evaluate symptoms in highly active individuals in the mistaken belief that high levels of fitness protect against rather than only reduce the risk of cardiac disease" p.2364* (Thompson et al., 2007)

Coronary heart disease (CHD) is a leading cause of death today, responsible for 20% of the deaths in the United States (Thom et al., 2006). Health care providers must determine an individual's cardiovascular (CV) risk accurately so treatment strategies, such as proper therapeutic lifestyle changes and pharmacological management are initiated. Establishing an individual's level of risk justifies aggressive treatment to prevent the progression of vascular and metabolic disease.

In the following pages is a discussion of CV risk, including comparison of several tools for global risk estimation. The methods used to measure the individual components of the tools used for global risk assessment are discussed, including blood pressure, obesity, lipid parameters, alterations in glucose metabolism, insulin resistance, and self-report measures. The chapter concludes with evaluation of a measurement tool for use in deployed military personnel assessing exposure to objective combat stressors and subjective responses using screening questions currently employed upon return from the theater of operations.

### Methods of Physiological Measurement

Precision and accuracy of physiologic measurements are essential. Terminology used to describe the reliability and validity of physiologic measures is different from the language used to evaluate psychometric properties of physical attribute measurement.

Terms used in the paper to describe physiologic measurement properties and their differentiation from psychometric properties are listed in at the end of this chapter.

## Measures of Global Cardiovascular Risk Assessment

Assessment of CV risk is a critical first step in developing a treatment plan for patients; however, primary prevention must not be made based solely on the percentage risk for a CV event. Care of the patient depends on a comprehensive history including all aspects of CV risk, only one of which is the selected CV risk assessment tool. Other areas of query include lifestyle risk factors and emerging risk factors ("Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection Evaluation And Treatment of High Blood Cholesterol In Adults (ATP III)", 2001) as well as the presence of insulin resistance. A summary of individual CV risk factors included in tools for global CV risk is listed in Table 1.

### *Framingham Risk Score*

The Framingham risk score (FRS) is the gold standard for comparison of alternate risk prediction tools. Predictive models for CHD were presented initially in 1991, based on data from the Framingham Heart Study and Framingham Offspring Study (N=5573) (Anderson, Odell, Wilson, & Kannel, 1991). The sample consisted of participants between the ages of 30 and 74 years who did not have CVD or cancer. After following the cohort for 12 years, a model combining the major risk factors of total cholesterol, high-density lipoprotein (HDL) cholesterol, blood pressure, smoking, glucose abnormalities, and left ventricular hypertrophy (LVH) was created to predict risk of

| | FRS (Wilson) (1998) | FRS (ATP III) (2001) | PDAY (2005) | SCORE (2003) | PROCAM (2001) | Metabolic Syndrome (2001) |
|---|---|---|---|---|---|---|
| **Age** | YES | YES | YES | YES | YES | NO |
| **Blood Pressure** | YES | YES | YES | YES | YES | YES |
| **Total Cholesterol/ LDL Cholesterol** | YES | YES | NO | YES | YES | NO |
| **Non HDL Cholesterol** | NO | NO | YES | NO | NO | NO |
| **HDL Cholesterol** | YES | YES | YES | NO | YES | YES |
| **Triglycerides** | NO | NO | NO | NO | YES | YES |
| **Smoking** | YES | YES | YES | YES | YES | NO |
| **Diabetes/Impaired Fasting Glucose** | YES | YES | YES | YES | YES | YES |
| **Body Mass Index/Waist Circumference** | NO | NO | YES | NO | NO | YES |
| **Insulin Resistance** | NO | NO | NO | NO | NO | YES/NO** |
| **Family History** | NO | NO* | NO | NO | YES | NO |
| **PREDICTION** | 10-year risk (%) of total CHD: angina pectoris, MI, and CHD (absolute risk and relative risk) | $\geq$ 2 risk factors, predicts 10-year risk (%) of hard coronary events, i.e., MI or CHD. Guides LDL cholesterol goals. | Probability (%) of target lesions in coronary arteries/ abdominal aorta | 10-year risk (%) of fatal CV event | 10-year risk (%) of hard coronary events, i.e., MI or sudden cardiac death | Increased risk of coronary heart disease*** |

**considered in the initial risk factor counting, but not as part of total score ** varies based on definition used ***variable risk assessments—refer to text. Abbreviations: FRS=Framingham risk score; PDAY= Pathobiological Determinates of Atherosclerosis in Youth; SCORE=Systematic Coronary Risk Evaluation System; PROCAM= Prospective Cardiovascular Münster Study*

**Table 1. Comparison of CV Risk Assessment Measures**

acute myocardial infarction (AMI), CHD, CHD death, CVD, CV death, and cerebrovascular accident in different age groups.

Modification of the FRS in 1998 incorporated recommendations from the National Cholesterol Education Program Adult Treatment Panel II and the Fifth Report of the Joint National Commission on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure (Wilson et al., 1998). Models predict the 10-year risk of CHD (%), including angina pectoris, AMI, and sudden cardiac death in individuals 30 to74 years of age. From this algorithm, both the 10-year absolute risk and relative risk can be determined. Because Framingham, Massachusetts is primarily a white, suburban population, concerns about its use in other populations arose. D'Agostino and colleagues (2001) validated the FRS in white and black American men and women; however, the tool consistently overestimated CV risk in Japanese-American men, Hispanic men and Native American women. Application of the FRS to German populations (N=14,468) (Hense, Schulte, Lowel, Assmann, & Keil, 2003) and a British male cohort (N=2732) (Cooper, Miller, & Humphries, 2005) also overestimated risk of hard CV endpoints.

The revised risk score incorporates most of the original variables and assigns points to each risk factor; the sum total score equates with a 10-year risk of CHD. Alternate tables allow risk calculation using either total cholesterol or low-density lipoprotein (LDL) cholesterol. The major difference in the revised model is the omission of LVH. While the presence of LVH is associated with hypertension and obesity (Haji et al., 2006), it may also be seen in athletes, also referred to as the "athlete's heart" (Sharma et al., 2002). The investigators acknowledge the association between LVH and hypertension, which is part of the model, but account for the omission by citing lack of

universal criteria for diagnosis of LVH (Wilson et al., 1998). From a practical standpoint, use of the new FRS is more feasible in the clinical setting, where time and logistics may preclude the use of electrocardiographs for routine purposes.

Most recently, the Framingham Heart Study investigators developed a general CVD algorithm, with all CV endpoints, including AMI, angina, coronary death, coronary insufficiency, hemorrhagic stroke, ischemic stroke, transient ischemic attack, intermittent claudication, and heart failure (D'Agostino et al., 2008). Additionally, a novel concept of "heart age/vascular age" is introduced. The algorithm transforms the age of an individual with CV risk factors into an age of an individual with the same risk, but with no risk factors. For a young cohort, such as military personnel, using the "heart age" may prove more useful than the FRS.

*Framingham Risk Score—ATP III Guidelines*

The NCEP/ATP III (2001) modified the FRS slightly. To determine appropriate goals for LDL cholesterol, the NCEP/ATP III recommends calculation of CV risk through assessment of major CV risk factors: age, premature CHD in a first degree relative, low HDL cholesterol, cigarette smoking, and hypertension (thresholds for the major risk factors is listed in Table 2). After a preliminary assessment of major risk factors, 10-year absolute risk for development of a CV event is calculated only in individuals with two or more risk factors (NCEP/ATP III, 2001). The authors suggest that in the absence of at least two major risk factors, an individual is likely low risk, i.e., < 10%. Individuals are stratified into three risk categories: high risk, >20%, intermediate risk, 10% to 20%, and low risk < 10%. Presence of CHD, diabetes, peripheral artery disease, abdominal aortic

aneurysm, or carotid artery disease automatically confers >20% risk in an individual. Stratification of individuals and changes in LDL cholesterol goals were modified in 2004 based on the results of several clinical trials. The high and low risk categories remained unchanged, however, intermediate risk was further stratified into 2 levels: moderate risk (2 or more risk factors with 10-year risk <10%) and moderately high risk (2 or more risk factors with 10 –year risk 10% to 20%) (Grundy et al., 2004).

There is concern, however, that FRS calculation only in the presence of two risk factors leads to misclassification of low risk individuals, and LDL cholesterol lowering therapy is therefore not implemented. Using NHANES data from 1999 through 2002 (N=4097), 5.3% of participants were misclassified as low risk individuals when indeed their risk was $\geq$ 10% (Persell, Lloyd-Jones, & Baker, 2006). While the majority of misclassified subjects had a risk of 10 to 12%, there was at least a 20% risk in 6.8% of this subset, most occurring in men between the ages of 40 and 64 years. The NCEP/ATP III FRS may not classify women into appropriate risk categories. Recently, Ridker and colleagues (Ridker, Buring, Rifai, & Cook, 2007) developed an algorithm incorporating both novel risk factors and family history to handle this shortfall.

*Limitations of Framingham Risk Scores*

Use of the FRS factors neither lifestyle risk factors, such as atherogenic diet, sedentary lifestyle, and obesity, nor emerging risk factors, such as impaired fasting glucose, homocysteine, lipoprotein (a) [Lp(a)], proinflammatory factors, and subclinical atherosclerosis (NCEP/ATP III, 2001). Consideration must be given to both lifestyle and emerging risk factors when assessing global CV risk and guiding interventions.

Additionally, the authors acknowledge the omission of BMI in the FRS, but indicate that it is difficult to quantify the contribution of obesity to CV events (Wilson et al., 1998), though few would argue that adipose tissue is metabolically active and contributes to CVD.

A concern for use of the FRS is that it may underestimate the risk for the military population. Misclassification into low risk categories may occur because of the negative points given for their young age; more significantly, FRS is not designed for individuals under the age of 30. Furthermore, calculation of absolute 10-year risk or relative risk may be misleading, and investigators advocate use of a "lifetime risk" instead, particularly to educate younger people who may find that a low relative risk is not enough to motivate adoption of therapeutic lifestyle modifications (Lloyd-Jones et al., 2006).

*Pathobiological Determinants of Atherosclerosis in Youth (PDAY)*

The PDAY study was a multicenter postmortem analysis of 15 to 34 year-olds who died from non-cardiac causes to determine risk factors associated with atherosclerosis (Zieske, Malcom, & Strong, 2002). Investigators identified atherosclerotic lesions in adolescents that were associated with the typical CV risk factors normally screened for at a later age (McMahan et al., 2005). This study led to the creation of a CV risk tool, targeting the younger population (n=1117 for coronary arteries; n=1458 for abdominal aorta). The risk score estimates the probability of a target lesion in the coronary arteries and the abdominal aorta. Target lesions are

operationally defined as either lesions with foam cells, a lipid core and a normal intima covering; or alternatively, a lipid core with calcification or a fibrous cap covering.

The scoring system was validated using a bootstrap technique, with a receiver operator characteristic (ROC) curve of .84 for abdominal aorta lesions and .78 for coronary artery lesions, indicating excellent and acceptable discrimination, respectively. Most recently, the tool was validated in a small postmortem sample of 15 to 34 year-olds (N=71); using only the modifiable risk factors, investigators validated the accuracy of the scoring tool in a postmortem analysis of 35 to 54 year-olds (N=141) (McMahan et al., 2006).

Using data from the Coronary Artery Risk Development in Young Adults study (N=2732-2975, depending on time point), the PDAY risk score predicted coronary artery calcium, a surrogate measurement of atherosclerosis (Gidding et al., 2006). The ROC curve for predicting coronary artery calcium was .736, which fared better than the FRS at .619.

*Systematic Coronary Risk Evaluation System (SCORE)*

Similar to the NCEP/ATP III, experts from European medical societies convened to develop CVD guidelines and created the SCORE assessment tool (De Backer et al., 2003). As with other tools, the SCORE is based on large prospective studies in European cohorts. The SCORE uses a low risk and a high risk algorithm. France, Belgium, Switzerland, Luxemburg, Spain, Portugal and Italy use the low risk algorithm, and all other European countries use the high-risk algorithm. Individuals are considered high risk when their 10-year risk is $\geq$ 5% because the SCORE calculates absolute risk of *fatal*

CV event, rather than including angina pectoris or non-fatal MI, as in other risk assessment tools.

*Prospective Cardiovascular Münster Study (PROCAM)*

The PROCAM study is a prospective cohort study conducted in Germany. Based on the 10-year follow up of men 35 to 65 years of age (N=5389), investigators created a scoring tool for CV risk assessment in men using independent predictors of AMI or sudden cardiac death (Assmann, Cullen, & Schulte, 2002). Ten-year risk falls on a continuum from < 1% to > 30%. Of all the assessment tools that offer predictive risk, this is the only one that incorporates both the presence of family history and triglycerides. While all of the risk estimations acknowledge that there may be a higher CV risk in the presence of a positive family history, and the NCEP/ATP III recognizes family history as a major risk factor, only the PROCAM assessment tool incorporates it into the total sum score. The ROC curve for predicting AMI or sudden cardiac death is .824, indicating excellent discrimination. In comparison, application of the FRS to this cohort resulted in a ROC curve of .778.

The tool is only for men, with a limited age range of 35 to 65 years. No validation studies in females were found. Although the majority of the military population is male, the gender and age restrictions limit its use in not only the military, but also for the general population.

*The Metabolic Syndrome*

The clustering of specific CV risk factors, including hypertension, hypertriglyceridemia, low high density lipoprotein cholesterol, abdominal obesity and

impaired fasting glucose, in various combinations, constitutes the metabolic syndrome. The metabolic syndrome as defined by NCEP/ATP III (2001) is included in this analysis because individuals are at increased CV risk when they meet the criteria for the diagnosis, i.e., the presence of at least 3 of 5 variables (Lakka et al., 2002; Wannamethee, Shaper, Lennon, & Morris, 2005; Wilson, D'Agostino, Parise, Sullivan, & Meigs, 2005). Investigators report a "metabolic score" or a "metabolic syndrome score" based on the number of risk factors present in an individual (Hunt, O'Malley, Feuerstein, & Taylor, 2003; Vidal et al., 2005). It stands in stark contrast to other risk assessment tools, however, because it does not project a consistent, predictive risk of a CV event or an atherosclerotic lesion. Perhaps in an effort to address this, investigators have applied the metabolic syndrome criteria to prospective cohort studies to determine its relationship to CVD. Using the Framingham Offspring Cohort (N=3323), Wilson and colleagues (2005) found a 2.5 fold increase (95% CI, 1.62-3.98) in total CHD (angina and hard endpoints) in participants who met criteria for the NCEP/ATP III metabolic syndrome during an 8 year period. In the San Antonio Heart Study (N=2372), participants free of CVD and diabetes, had a 2 fold increase (95% CI, 1.13-3.57) in CV mortality during a 12 year follow up period (Hunt, Resendez, Williams, Haffner, & Stern, 2004). In a meta-analysis of longitudinal studies of the metabolic syndrome (N=36), individuals meeting the criteria for the metabolic syndrome had 1.78 relative risk (95% CI, 1.58-2.00) of coronary death and CV events (Gami et al., 2007).

Whether the 16 various combinations of the metabolic syndrome carry the same CV risk remains questionable (Kahn, Buse, Ferrannini, & Stern, 2005), and there are

questions regarding the selection of variables for inclusion in the metabolic syndrome (Reaven, 2005). Presumably, the physiological abnormalities of the metabolic syndrome are related to the presence of insulin resistance, which itself is a significant risk factor for CVD (Facchini, Hua, Abbasi, & Reaven, 2001; Facchini, Stoohs, & Reaven, 1996; McLaughlin & Reaven, 2003; Reaven, 2002; Reaven, 1988). There is concern, however, that the NCEP/ATP III criteria may not capture those who are truly insulin resistant. Reaven (2004) writes that insulin resistant individuals may not meet the criteria for inclusion in the NCEP/ATP III definition for the metabolic syndrome. Investigators have reported a low sensitivity of 20 to 50% but a high specificity of > 90%, to determine insulin resistance in subjects who meet the NCEP/ATP III criteria for the metabolic syndrome (ROC curve: .65). Though the authors note the significant limitations due to the homogeneity of the sample and small sample size (Liao et al., 2004), the findings were replicated in larger studies, but with a sensitivities and specificities ranging between 42% and 94%, respectively (N=256) (Sierra-Johnson et al., 2006) and 46% and 93%, respectively (N=443) (Cheal et al., 2004).

## Measurement of Components of Cardiovascular Risk Measures

Methods of measurement of biologic risk factors included in the global CV estimation follows. The generally accepted cut points for determining increased CV risk are listed in Table 2, though it is important to note these values must be viewed in the context of the presentation of the patient and existing co-morbidities.

*Blood Pressure*

For accurate blood pressure assessment, the patient sits for at least 5 minutes in a chair, feet flat on the floor and the arm at heart level. The blood pressure cuff is inflated, and the pressure is released slowly. Identification of the first and last Korotkoff sounds indicates the

| Risk Factor | Levels Conferring Increased CV Risk |
|---|---|
| **Age** | Men: ≥ 45 years; Women: ≥ 55 years [1] |
| **Blood Pressure** | Systolic BP: ≥ 140 mmHg; Diastolic BP: ≥ 90 mmHg [2] |
| **Total cholesterol or LDL cholesterol** | Total Cholesterol: ≥ 200 mg/dl; LDL Cholesterol: ≥ 160 mg/dl [1] |
| **Non-HDLCholesterol** | ≥ 190 mg/dl [1] |
| **HDLCholesterol** | < 40 mg/dl [1] |
| **Triglycerides** | ≥ 150 mg/dl [1] |
| **Smoker** | Current smoker [1] |
| **Diabetes/Impaired Fasting Glucose** | Impaired Fasting Glucose: ≥ 100-125 mg/dl; Diabetes: ≥ 126 mg/dl |
| **BMI/Waist Circumference** | ≥ 25 kg/m² */Waist circ: Men: ≥ 40 inches; Women ≥ 35 inches [1] |
| **Insulin Resistance** | No standardization [3] |
| **Family History** | Positive family history in first degree males < 55 years; positive family history in first degree females < 65 years [1] |

[1](NCEP/ATP III, 2001) [2](National Heart Lung and Blood Institute, 2003) *(NHLBI, 1998) [3] Detailed explanation of measurement follows

**Table 2 Individual Cardiovascular Risk Factors**

systolic and diastolic blood pressure, respectively. The average of two measurements is recorded (National Heart Lung and Blood Institute, 2003) using an appropriate sized cuff in accordance with established guidelines (Pickering et al., 2005).

Minimizing both systematic error and random error when measuring physiologic parameters is important (Engstrom, 1988). Calibration of blood pressure equipment with another device and establishing a detailed and specific protocol for assessment of blood pressure that addresses technique and patient preparation reduces systematic error by ensuring consistent measurements (Hulley, Cummings, Browner, Grady, & Newman, 2007). Limiting the variability in a patient's readings minimizes random error. Such measures include not taking the blood pressure in an agitated or anxious individual and calculating the mean of two blood pressure measurements with at least one minute between readings (Pickering et al., 2005).

*Obesity*

Body mass index is the relationship of height and weight ($kg/m^2$) and estimates an individual's body fat. The BMI values for overweight and obese individuals are $\geq 25$ $kg/m^2$ and $\geq 30$ $kg/m^2$, respectively (National Heart Lung and Blood Institute, 1998). While BMI is accepted as an easy and feasible method to stratify normal weight, overweight, and obese individuals, there are populations in which this may not hold true (Prentice & Jebb, 2001).

Surrogate measures of waist circumference and waist-hip ratio are suggested measurements of obesity. However, rather than a universal threshold for waist circumference, investigators suggest variable waist circumferences within BMI

categories discriminate risk of CVD better than a universal threshold for all BMI categories (Ardern, Janssen, Ross, & Katzmarzyk, 2004). Moreover, thresholds meeting the criterion for enlarged waist circumference are not applicable across all ethnicities, (Alberti, Zimmet, & Shaw, 2006), affecting the ease of its use.

To measure waist circumference according to National Institute of Health guidelines (1998), a horizontal mark is placed at the uppermost border of the right iliac crest, with a perpendicular line placed at the right mid axillary region. Placing the tape measure snugly around the waist and parallel to the floor, the measurement is made at the cross hair during "normal minimal respiration".

*Blood Lipid Measurements*

Lipoproteins are the transport mechanism for cholesterol and triglycerides in the body. The six classes of lipoproteins include chylomicrons, very low-density lipoprotein (VLDL), intermediate density lipoprotein (IDL), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and Lp(a) (Tulenko & Sumner, 2002). Discussion is limited to those included in CV risk assessment tools.

*Low-density Lipoprotein Cholesterol* Low-density lipoprotein cholesterol is expressed in mg/dl and is measured indirectly or directly. Indirect measurement is calculated using the Friedewald equation:

**(LDL-Cholesterol) = (Total Cholesterol) – (HDL-Cholesterol) – (Triglycerides)/5**

If triglycerides exceed 400 mg/dl LDL cholesterol calculation is inaccurate. Direct measurement of LDL using ultracentrifugation and precipitation (ß quantification) or other direct method of measurement is preferred, however, because calculated LDL

cholesterol tends underestimate the actual value. Mean physiologic variation of LDL cholesterol is 8.2%, with a range of approximately 6-11% (Bachorik & Ross, 1995). Diet, obesity, smoking, exercise, and alcohol intake affect LDL cholesterol metabolism (G. R. Cooper, Myers, Smith, & Schlant, 1992). For accurate assessment, LDL cholesterol is collected after a 12 hours fast, but may be collected after a 9 hour fast. Acceptable coefficient of variation for LDL cholesterol is $\leq$ 4%, an acceptable bias for LDL cholesterol is also $\leq$ 4%, and total error should not exceed 12% (Bachorik & Ross, 1995).

Low-density lipoprotein particles are heterogeneous, comprised of atherogenic small, dense LDL particles (pattern B) and large, buoyant LDL particles (pattern A). The vertical auto profile test (Kulkarni, 2006), electrophoresis, or nuclear magnetic resonance spectroscopy (Witte et al., 2004) are methods to determine particle size.

*High-density Lipoprotein Cholesterol* High-density lipoprotein cholesterol is expressed in mg/dl and is measured using a variety of techniques, including density gradient ultracentrifugation, electrophoresis, liquid chromatography, chemical precipitation, and direct HDL cholesterol assays (Langlois & Blaton, 2006). The physiologic variation of HDL cholesterol is approximately 7.5%, with values affected by alcohol use, diet, smoking, changes in weight, and level of physical activity. High-density lipoprotein cholesterol is collected after at least 9, but preferably 12 hours of fasting. Acceptable coefficient of variation for HDL cholesterol is $\leq$ 4 % and bias is $\leq$ 5 %; total error should not exceed 13% (Warnick, 2000).

*Triglycerides* Triglycerides are the primary components in chylomicrons and VLDL and comprised of a glycerol molecule and 3 fatty acids. Values are expressed in mg/dl and

are measured in the laboratory using complex enzymatic methods (Stein & Myers, 1995). The biologic variation of triglycerides is approximately 23.7%, and is affected greatly in a non-fasting state. Triglycerides are collected after a 12 hour fast, but may be collected as early as 9 hours after fasting. Acceptable coefficient of variation and bias for triglycerides is $\leq$ 5% (Warnick, 2000).

*Non-High-density Lipoprotein Cholesterol* Non-HDL cholesterol is calculated by subtracting HDL cholesterol from the total cholesterol. If bias is associated with HDL cholesterol, there will also be bias in non-HDL cholesterol value.

*Diabetes/Impaired Fasting Glucose*

Diagnostic criteria for diabetes includes: (1) random glucose measurement of $\geq$ 200 mg/dl along with polyuria, polydipsia, and inexplicable weight loss; (2) a fasting ( $\geq$ 8 hours) blood glucose $\geq$ 126 mg/dl; or (3) presence of a glucose measurement $\geq$ 200 mg/dl 2 hours after a 75 gram oral glucose load (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003). Repeating one of the diagnostic methods on a different day is required to confirm the diagnosis. Impaired fasting glucose was defined a fasting glucose between 110 and 125 mg/dl, however, in a follow up report, the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus lowered the threshold to $\geq$ 100 mg/dl (Genuth et al., 2003).

In the laboratory, glucose is quantified using an enzymatic reaction method. Point of care testing with portable blood glucose monitors also use enzymatic methods, primarily a glucose oxidase reagent. Confounding patient factors (hydration, oxygenation) and lack of compliance with acceptable variability and coefficient of

variation limits is sometimes problematic (Dungan, Chapman, Braithwaite, & Buse, 2007). The Ascensia Contour (Bayer, Tarrytown, NY) uses glucose dehydrogenase and is not affected by oxygenation; arterial, venous, and capillary blood sources provide comparable results (Frank, Rivera, Wallace, & Parkes, 2007). Using venous blood, the Contour has an acceptable coefficient of variation of 4.2%. Accuracy is demonstrated using an error grid analysis with 97.9 % of specimens falling within zone A, or ± 15% or ± 10 mg within the laboratory measurements. This meets the American Diabetic Association recommendations of 5% coefficient of variation, but exceeds the recommendations for total variability of < 10% ("Consensus statement on self-monitoring of blood glucose", 1987).

*Insulin Resistance*

It is important for the clinician to be aware of a patient's insulin sensitivity because insulin resistance carries a great risk of CVD (T. McLaughlin et al., 2003; Reaven, 2002); however, measurement of insulin resistance is not practical in the clinical setting. First, there are a number of complex methods to quantify insulin resistance, both directly and indirectly. Second, rates of insulin mediated glucose uptake may vary 10 fold in healthy individuals (Reaven, 2002), with no absolute cut points for the classification of insulin resistance using any method (Reaven, 2005). Though the euglycemic-hyperinsulinemic glucose clamp technique (clamp technique) is often referred to as the "gold standard" for measuring an individual's glucose disposal rate, there are no established thresholds for defining insulin resistance using this method (Liao et al., 2004). The difficulty of identifying individuals who are insulin resistant is managed by stratifying individuals in

the highest tertile or quartile in a given study population. A demarcation between the most insulin sensitive and the most insulin resistant in a population can be made, with individuals in the latter group exhibiting greater CV risk and CVD. In one prospective study, investigators found that after a mean follow-up of 6.3 $\pm$ 0.2 years (range: 4-11 years) of healthy individuals (N=647), those in the highest quartile of insulin, post glucose load, had significant increases of impaired glucose tolerance, type 2 diabetes, hypertension, and CHD when compared to those in the first three quartiles (Zavaroni et al., 1999). Similarly, over a 6 year period, investigators in another study identified significant increases of stroke, type 2 diabetes, CHD, and hypertension in the most insulin resistant tertile using the insulin suppression test (Facchini, Hua, Abbasi, & Reaven, 2001).

Finally, procedures for measuring hyperinsulinemia or insulin resistance may vary between laboratory facilities, so individual tests might have inconsistent values when tested at different laboratory facilities (Kahn, Buse, Ferrannini, & Stern, 2005; Tuan, Abbasi, Lamendola, McLaughlin, & Reaven, 2003). To this end, investigators suggest that commercial laboratories provide not only requested insulin levels, but also the distribution of all levels tested at their facility to give reference points for interpretation (Tuan, Abbasi, Lamendola, McLaughlin, & Reaven, 2003).

Direct measurements of insulin mediated glucose uptake include the clamp technique, the insulin suppression test (IST), the minimal model analysis of the frequently sampled intravenous glucose tolerance test (minimal model), and the insulin tolerance test. Because the insulin tolerance test is used infrequently, it is omitted from

the comparative analysis. Indirect methods employed to assess insulin resistance include the homeostasis model assessment for insulin resistance (HOMA-IR), the quantitative insulin sensitivity check index (QUICKI), fasting insulin, and insulin levels, post glucose load, to name a few.

Though used often when comparing different methods of measurement, correlation coefficients do not provide an assessment of agreement between two methods of measurement; Pearson's correlation simply identifies the strength of association between two measures (Bland & Altman, 1986). Rather, Bland and Altman (1986) suggest that differences expressed as "bias" is a more appropriate analysis when considering alternative methods of measuring a variable. An important assumption in using this method, however, is the use of the same unit of measurement between methods. With different units of measurement, correlation coefficients are indeed useful to describe the percent variance accounted for in a specific method with an alternate technique. Comparison studies of insulin resistance generally utilize correlation coefficients and ROC curves (Abbasi & Reaven, 2002;Hays et al., 2006;Katz et al., 2000; McAuley et al., 2001;Tuan, Abbasi, Lamendola, McLaughlin, & Reaven, 2003;Vaccaro et al., 2004).

*Direct Measurements of Insulin Resistance* The direct methods of measuring insulin resistance are complex, expensive, and invasive. The IST is a method that uses steady state plasma glucose (SSPG) to estimate the degree of insulin resistance (Greenfield, Doberne, Kraemer, Tobey, & Reaven, 1981). Infusion of somatostatin, insulin, and glucose occurs over a 3-hour period, and blood is sampled throughout the infusion to

measure the SSPG at various time points. The average of the last series of blood measurements determines an individual's SSPG. Values of SSPG are divided into tertiles based on the prospective studies previously described, with the most insulin sensitive individuals within a study in the lowest tertile and the most insulin resistant individuals within a study in the highest tertile (Tuan, Abbasi, Lamendola, McLaughlin, & Reaven, 2003).

The clamp technique also involves multiple infusions. A steady state of insulin is infused with glucose administered at variable rates in order to maintain constant glucose levels throughout the procedure equivalent to the individual's fasting glucose levels. After approximately 2 to 3 hours, the glucose rate is stabilized; insulin resistance is estimated by the rate of glucose infusion divided by the insulin level. Endogenous insulin production is not inhibited for the procedure, presumably a large source of variation in the population (Radziuk, 2000).

Finally, the minimal model measures insulin sensitivity using a mathematical model. After a glucose load, blood is sampled multiple times over a 180-minute period to assess the concentrations of glucose and insulin. Modifications to the test have evolved, incorporating administration of insulin or tolbutamide 20 minutes after the glucose load (Pacini et al., 1998).

*Comparison of Direct Methods* To compare the effectiveness of different direct methods in determining insulin sensitivity, investigators conducted a meta-analysis of minimal model techniques versus the clamp technique (Gordillo-Moscoso, Valadez-Castillo, Mandeville, & Hernandez-Sierra, 2004). There is a moderate correlation (r= .61-

.65) between the minimal model variants using tolbutamide or insulin and the clamp method. While Bland-Altman plots illustrated small mean differences between the clamp and the minimal model variant using tolbutamide, the concordance limits, or "limits of agreement" (mean $\pm$2 SD) (Bland & Altman, 1986) were large, indicating large variation between methods. The mean differences between the clamp and the minimal model variant using insulin were significantly different, indicating that this method was not equivalent to the clamp technique.

The accuracy and precision of the IST was established using duplicate measurements and correlation with the clamp technique (Greenfield, Doberne, Kraemer, Tobey, & Reaven, 1981). A significant, high correlation (r=.93) between the clamp technique and the IST in obese and non-obese participants with both normal and impaired glucose tolerance, i.e., the SSPG values accounted for 86.5% of the variance in the clamp technique. In this study, the IST was repeated on 14 subjects on separate occasions, with no significant differences between values in those who were most insulin resistant and those who were most insulin sensitive.

From these comparisons, it would appear that the IST and clamp technique are most accurate methods for direct measurement of insulin resistance over the minimal model. From a practical standpoint, however, the IST is best suited for clinical research studies. Constant infusion rates of glucose and insulin minimizes error that may occur with the use of a test requiring constant changes in infusion rates. Additionally, suppression of endogenous insulin production when performing the IST eliminates it as a confounding factor in SSPG levels, a factor not addressed in the clamp technique. For

these reasons, rather than comparing various indirect measures with each of the direct methods, the referent method for assessment of insulin sensitivity will be the IST.

*Indirect Methods of Insulin Measurement* The homeostasis model assessment for insulin resistance (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI) are indirect methods of insulin sensitivity using the following equations:

**HOMA-IR= (fasting glucose X fasting insulin)/22.5**

**QUICKI= 1/[log(fasting insulin) + log(fasting glucose)**

(Radziuk, 2000)

Measurements of fasting insulin and insulin, post two hour glucose load are straightforward.

A moderate correlation (r=.64) exists between IST and HOMA-IR in a healthy, non-diabetic population (Abbasi & Reaven, 2002). Correlations between IST and QUICKI were similar: r= -.54 in non-diabetic hypertensives (Hwu et al., 2007) to r=-.60 in a non-diabetic population (Abbasi & Reaven, 2002). Fasting insulin levels are moderately correlated with the IST (r=.61), similar findings with the 2 hour insulin post glucose load (r=.62) (Yeni-Komshian, Carantoni, Abbasi, & Reaven, 2000) Despite these moderate to high correlations, consideration of BMI is essential when using surrogate measures. Body mass index modifies the relationship between IST and fasting insulin, HOMA-IR, and QUICKI, with obese individuals showing a stronger association than normal weight individuals (Kim, Abbasi, & Reaven, 2004). An exception to this was found in the insulin levels after a glucose load, which was similar across BMI categories.

If identification of insulin resistant individuals who are susceptible to CVD is the

goal using fewer measures or more easily obtained measures, precise and accurate techniques must be developed and implemented. Simplifying the diagnostic criteria for insulin resistance to the use of an easily obtained measure would be useful. In an analysis of 3 cohorts (N=1594), triglyceride/HDL-C ratios $\geq$ 3.5 correlate to SSPG as well as fasting insulin levels (r=.60). Analysis of ROC curves was between .84 and .91 in each of the 3 cohorts studied. Moreover, a greater correlation is seen between SSPG and triglycerides alone (r=.57) using the IST (McLaughlin et al., 2005) than is seen between glucose disposal rate and triglycerides (r= -.40) using the clamp technique (Liao et al., 2004).

*Smoking Status*

Ascertainment of smoking status is helpful to determine CV risk, however, there is a tendency for patients to over report "desirable" traits (Holtgraves, 2004). Information bias may operate in a number of ways when answering a question: (1) information may be retrieved, carefully processed, then answered based on social desirability; (2) information is not retrieved at all, and the information is provided solely based on what is socially acceptable; or (3) the individual selectively recalls information and answers the self- report measure in the most positive way (Holtgraves, 2004).

The findings of the accuracy of self-report of smoking status are conflicting. Large epidemiologic studies suggest that use of self-report measures for smoking assessment is accurate. Using NHANES III data (N=15,357), researchers found only a 1.4% discrepancy between self- report of non-smoking and serum cotinine levels $\geq$ 15 ng/ml (Caraballo, Giovino, Pechacek, & Mowery, 2001). Interestingly, 7.5% of self-

reported smokers did not have serum cotinine levels ≥15ng/ml. In a smaller study of participants presenting for preoperative screening (N=100), researchers identified much higher rates of discrepancy: 37% of self-reported non-smokers tested positive for urine cotinine, and similar to the NHANES study, 7% of self-reported smokers tested negative for urine cotinine (Payne & Southern, 2006).

In a meta-analysis on the validity of self-reported smoking verified by biochemical measures, the sensitivity range was 6 to 100%, with a mean sensitivity of 87.5% (Patrick et al., 1994). The specificity range was 33 to 100% with a mean specificity of 89.2%. Greater sensitivity was found in observational versus interventional studies and with interviewer administered versus self-administered questionnaires.

*Family History of Premature Cardiovascular Disease*

A positive family history of CVD is defined as premature cardiac disease in first-degree male relatives ≤ 55 years or first-degree female relatives ≤ 65 years. Evidence exists that family history of cardiac disease independently predicts CV events (Eaton et al., 1996) and may act synergistically with traditional risk factors in CAD (Leander, Hallqvist, Reuterwall, Ahlbom, & de Faire, 2001). Accuracy of self-report of parent and sibling history of CHD had sensitivities of 85% and 81%, respectively; specificity was 93% and 98%, respectively (Bensen et al., 1999).

## Measurement of Stress

There is a documented association between psychological stress and CAD (Meisel et al., 1991; Rosengren et al., 2004; Strike et al., 2006), however, the relationship between both acute and chronic stress and CAD in military personnel

deployed in the Global War on Terror (GWOT) is unknown. To explore this question, a quantifiable measure of combat stress experienced during deployment is necessary.

*Global War On Terror Stress Score* In an effort to identify service members who need either medical referrals or psychological counseling upon redeployment, the Army mandates that all service members complete a Post Deployment Health Assessment, a comprehensive questionnaire specific to medical conditions, exposures, and experiences during a deployment. Of interest for this dissertation are the questions specific to combat exposure and psychological and behavioral responses to stressors experienced during their deployment (Table 3), from this point forward referred to as the "GWOT Stress Scale".

The use of the GWOT Stress Scale is not ideal to assess combat stress, but it is clearly the most feasible way to determine stress burden retrospectively. The most significant limitation is that the there are no studies on its reliability and validity. The eight questions measure three constructs: combat experience (questions 1-2), perceived threat (question 3) and physical and psychological responses to the combat experience (questions 4-8).

Questions 1-3 in the GWOT Stress Scale are similar to questions from the Combat Exposure Scale, a 7-item questionnaire developed for use in clinical research of PTSD and designed to categorize combat exposure, ranging from light to heavy (Keane et al., 1989). The tool was assessed for reliability and validity in a sample of Vietnam veterans (N=362). Cronbach's alpha was .85, and test-retest reliability was .97. Criterion validity was established through moderate correlation with the Mississippi

Post Traumatic Stress Scale (r=.43). Construct validity was further established by determining divergent validity, comparing scores of individuals with known PTSD and

1. Did you see anyone wounded, killed, or dead during this deployment? *(mark <u>all</u> that apply)*
___ No (0) ___ Yes (___ Coalition ___ Enemy ___ Civilian) (1)

2. Were you engaged in direct combat where you discharged your weapon?
___ No (0) ___ Yes (___ land ___ sea ___ air) (1)

3. During this deployment, did you ever feel that you were in great danger of being killed?
___ No (0) ___ Yes (1)

4. Are you currently interested in receiving help for a stress, emotional, alcohol, or family problem?
___ No (0) ___ Yes (1)

5. Have you ever had any experience that was so frightening, horrible, or upsetting that IN THE PAST MONTH you have had any nightmares about it or thought about it when you did not want to?
___ No (0) ___ Yes (1)

6. Have you ever had any experience that was so frightening, horrible, or upsetting that IN THE PAST MONTH you tried hard not to think about it or went out of your way to avoid situations that remind you of it?
___ No (0) ___ Yes (1)

7. Have you ever had any experience that was so frightening, horrible, or upsetting that IN THE PAST MONTH you were constantly on guard, watchful, or easily startled?
___ No (0) ___ Yes (1)

8. Have you ever had any experience that was so frightening, horrible, or upsetting that IN THE PAST MONTH you felt numb or detached from others, activities, or your surroundings?

___ No (0) ___ Yes (1)

**Total Score _____ (0-8)**

**Table 3 Global War on Terror Stress Scale**

those who did not have PTSD; as expected, PTSD veterans scored significantly higher on

the scale (Keane et al., 1989).

Questions 5-8 are similar to questions from the Post Traumatic Checklist-Military (PCL-M), a 17-item self-report screening tool for PTSD. The questions in the GWOT Stress Scale have at least one question in each of the three domains the PCL-M was designed to measure, including re-experiencing symptoms, avoidance or psychic numbing, and hyperarousal symptoms (Weathers, Litz, Herman, Huska, & Keane, 1993). On the PCL-M, a likert scale is used for scoring, with a range of 1-5 ("not at all" to "extremely") for each question; this differs from the dichotomous questions asked on the GWOT Stress Scale. On the PCL-M, scores may range between 17 and 85, with a score of $\geq$ 50 indicating the presence of PTSD. The PCL-M has been validated in a sample of Vietnam veterans (N=123) and Gulf War I veterans (N=1006).

The reliability and validity statistics of the PCL-M are excellent. Internal consistency of the PCL-M was demonstrated with an overall Cronbach's alpha of .96 and .97 in each of the different veteran's groups, though suggests redundancy of the questions; test-retest reliability was .96 (Weathers, Litz, Herman, Huska, & Keane, 1993). Criterion validity was established by comparing the PCL-M to a "gold standard", in this case, the Structured Clinical Interview for DSM III. Using a cutoff score of 50, the kappa statistic was .64, indicating good agreement and an optimal sensitivity of 82% and specificity of 83% to determine the presence of PTSD. Construct validity was established by measuring the PCL-M against several post-traumatic checklists to determine convergent validity. The tool had moderate to high correlations among them, including the Mississippi Post Traumatic Scale (r=.93), Impact of Events Scale (r=.90), and the

Combat Exposure Scale (r=.46).

The "Deployment Risk and Resiliency Inventory (DRRI)" (King, King, & Vogt, 2003) was developed in response to interests in war zone stressors and how they affected the physical and mental health of military personnel. Existing measures of stress and combat exposure developed in the Vietnam War era lack consideration of the unique stressors present in modern day operations. The DRRI has 14 subscales; the subscales may be administered together or separately in any combination. Three scales were of interest for the dissertation study: *Deployment Concerns* (construct: perceived threat), *Combat Experiences* (construct: combat exposure), and *Post Battle Experiences* (construct: exposure to consequences of combat). The subscales each have 15 items, with Deployment Concerns scored on a 1-5 likert scale (strongly agree-strongly disagree), and Combat Experiences and Post Battle Experiences scored as dichotomous, yes/no response. There is no threshold for any of these subscales; higher scores indicate greater perceived threat, combat exposure, or exposure to the aftermath of combat experiences. The tool was tested in a sample (N=495) of Gulf War I veterans. Internal consistency was .89 for Deployment Concerns and Post Battle Experiences and .85 for Combat Experiences. In this dissertation, internal consistency was assessed in a sample of healthy male volunteers (N=138) returning from deployment overseas. For this group, internal consistency was acceptable for Deployment Concerns ($\alpha$=.77), good for Combat Experiences (KR20=.89), and Post Battle Experiences (KR20=.92), though the higher values suggest there is redundancy in the questions.

To establish construct validity of the DRRI, the authors examined relationships between the subscales and other tools measuring physical and mental health outcomes and neurocognitive deficits in a sample of Gulf War I veterans (N=357). While physical health outcome measures were consistently correlated in the low to moderate range (r=.24-.52) for Deployment Concerns, both the Combat Experience and Post Battle Experience subscales had no to low correlations (.05-.32). The highest correlation between the three subscales was with PTSD (r=.28-.52) (King, King, & Vogt, 2003).

The GWOT Stress Scale has a possible range of 0 to 8. Higher total scores indicate greater exposure to events or experiences that may contribute to stress and subsequent responses during a deployment. The underlying assumption of the highest scores representing greater stress is that all individuals perceive threat and/or manifest a psychological response to objective combat stressors. Such an assumption is not necessarily valid and it is particularly problematic in a military population that likely under reports psychological symptoms. Using the GWOT Stress Scale to measure stress is indeed a limitation and a measurement tool with established psychometric properties is preferable. Without interviewing individuals, however, it is clearly the most feasible measure available to obtain an objective measure of actual combat experience, perceived threat, and responses to the deployment. The ability to quantify combat exposure and both physical and psychological responses is important to determine relationships between health outcomes and stress exposure.

To establish psychometric properties of the GWOT Stress Scale, the tool was administered along with three subscales from the DRRI to a healthy group of service

personnel returning from an overseas deployment (N=138). The answers to the pencil and paper GWOT Stress Scale were compared with the computer version to determine test-retest reliability statistics. The interval between the two tests varied from 0-6 months (mean 1.5 months), with many completed prior to redeployment to the United States. It is plausible that answering questions while still in a combat zone may bias an individual's answers, therefore the test-retest reliability must be interpreted with caution. Additionally, not all participants had a comparison score (n=8) because the deployment location was classified. While the variable time interval and missing data pose limitations of the psychometric analysis, the test-retest reliability was satisfactory (r=.76) and had acceptable internal consistency (KR 20=.76).

The GWOT Stress Scale does not comprise a formal instrument, but the questions have face validity. Concurrent validity of the GWOT Stress Scale was demonstrated with moderate correlation with the Combat Experiences subscale (r=.61) and Post Battle Experiences subscale (r=.56); the Deployment Concerns subscale had only a low correlation (r=.40). This is likely due to the GWOT Stress Scale only having one question associated with the construct of perceived threat ("Did you feel in danger of being killed?"). A point biserial analysis of the Deployment Concerns subscale and this individual question improved the correlation (r=.48). It could be argued that the GWOT Stress Scale measures primarily objective experiences and objective responses to stress and therefore the low correlation of the Deployment Concerns subscale represents a form of divergent validity. While this tool clearly does not perform ideally, the tools for measuring combat stress is limited to this and PTSD scales that do not capture the

nature of today's GWOT. Finally, the GWOT Stress Scale scores were significantly different between those in direct combat situations (Iraq and Afghanistan) and other GWOT locations that have presumably less hostile actions (1.00 vs. 2.32, p=.03), suggesting the questions can discriminate between areas which likely have higher environmental stressors.

In a preliminary analysis of the relationship of stress and ACS, data were examined on 201 cases (n=67) and controls (n=134) matched on age ( $\pm$ 5 years) and ethnicity, stress scores were available on 35 cases and 70 matched controls. Approximately 20% in both cases and controls reported a "zero" sum total score, limiting its use. For this reason, a decision to use a median split, divided the group into 2 groups; using a score of 0-2 indicated "low stress" and 3 and higher indicated "high stress". The dichotomous stress score was significantly different between cases and controls in the univariate conditional logistic regression analysis (OR 3.17, 95% CI, 1.19, 8.43). More importantly, use of the dichotomous variable remained significant in the multivariate logistic regression analysis (OR 12.12, 95% CI 1.15, 128.47), adjusting for age, family history of premature CAD, history of hypertension, dyslipidemia, smoking, and BMI. These findings show that stress as measured by the GWOT Stress Scale independently predicts ACS in service members deployed in the GWOT.

## Conclusion

Global CV risk estimation includes anthropometry, physiologic measurements, and biomarkers to calculate risk. Acute coronary syndrome is also associated with acute and chronic stress, an often overlooked tenet. While much of the CV risk comes with

advancing age, a problem not faced by the majority of the military population, risk factors such as obesity, smoking and family history of premature CAD exist in military members. There are a number of CV risk tools, and despite its limitations, the FRS (Wilson et al., 1998) provides the most comprehensive screening assessment of CV risk. Awareness of the variability in measurements of the FRS components is essential. Risk scores are a useful adjunct to determine an individual's risk and level of intervention in order to prevent the onset or progression of CVD. Other traditional and emerging CV risk factors, such as obesity, sedentary lifestyle, and subclinical atherosclerosis are not part of the FRS algorithm, but must be considered in global risk assessment. A critical omission of all CV risk tools is insulin resistance; it is especially important because the physiologic changes associated with hyperinsulinemia including hypertension, dyslipidemia, endothelial dysfunction, and hyperglycemia, put an individual at increased CV risk. Despite the difficulty in direct measurement of insulin resistance, surrogate markers are useful and can be used in the primary care setting.

Despite the limitations of the GWOT Stress Scale, measuring exposure to stress during a deployment is essential to establish relationships between CV risk and acute CV events. In a preliminary analysis, the measure of the construct, "combat stress" using the GWOT Stress Scale is independently associated with the occurrence of ACS. Combat duty in a highly stressful war zone in a vulnerable individual may create the "perfect storm", and thorough predeployment CV risk screening can potentially modify one's risk, or more importantly, thwart an acute CV event.

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Measurement terms

***Accuracy*** refers to the extent to which a measurement accurately estimates what it is intended to estimate, and is affected by systematic error, i.e., subject, instrument, or observer bias (Hulley, Cummings, Browner, Grady, & Newman, 2007). Accuracy cannot be achieved without precision (Warnick, 2000) Accuracy (validity) of physiologic measurements is demonstrated through contrasting groups with known values, correlating measures to gold standards, and using ROC curves (Frank-Stromberg & Olsen, 1992).

***Bias*** is the "consistent or systematic differences between the measured values and the reference value" (Warnick & Wood, 1995) . Bias that is systematic may also be referred to as systematic error (Last, Spasoff, Harris, Thuriaux, & International Epidemiological Association., 2001).

***Coefficient of Variation*** is a way of expressing variability in a measurement. The standard deviation is divided by the mean to obtain a percentage, thereby standardizing the standard deviation to allow for comparisons (Reed, Lynn, & Meade, 2002). The coefficient of variation may be thought of as the imprecision of the measurement (Warnick, 2000), or the reliability.

***Physiologic Variations*** are conditions that affect the measurement of lipids (Cooper, Myers, Smith, & Schlant, 1992). Behavioral mechanisms, such as diet, obesity, smoking, exercise, and alcohol intake can affect the results of a lipid panel; clinical conditions such as acute MI, stroke, insulin resistance, infections, and medications also influence lipid metabolism. Fasting, non-fasting, prolonged fasting, and posture are also

implicated in changes in lipids. Physiologic, or biologic, variation of lipids is expected and clearly variable, depending on the lipid parameter of interest.

***Precision*** refers to reproducibility of a measurement and is affected by random error, i.e., variability in the subject, instrument, or observer (Hulley, Cummings, Browner, Grady, & Newman, 2007). Precision (reliability) of physiologic measurements is demonstrated through mean measurements, duplicate measurements, coefficient of variation, and standard error (Frank-Stromberg & Olsen, 1992).

***Receiver operator characteristic (ROC) curve*** is a graphical display of whether a test can discriminate between those with and without the condition of interest (Last, Spasoff, Harris, Thuriaux, & International Epidemiological Association., 2001). The ROC curve may be quantified, in which values of 0.5 imply discrimination by chance and a value of 1.0 reflects perfect discrimination (Meigs, 2004).

***Reliability*** is a method of assessing whether a measurement tool captures the "true score" of the individual as opposed to error (Switzer, Wisniewski, Belle, Dew, & Schultz, 1999); also the repeatability of an instrument indicates high reliability (Nunnally & Bernstein, 1994). Reliability may be measured (1) through levels of internal consistency, or to what degree the items in a measurement measure the same concept or (2) through consistency of repeated measurements i.e., test-retest, inter-rater reliability, intra-rater reliability, split half, and alternative form (Switzer, Wisniewski, Belle, Dew, & Schultz, 1999).

***Sensitivity*,** or the true positive rate, is the proportion of people who actually have a disease who are correctly identified: true positive/true positive + false negative (Last, Spasoff, Harris, Thuriaux, & International Epidemiological Association., 2001).

***Specificity*,** or the true negative rate, is the proportion of people who do not actually have the disease who are correctly identified: true negative/true negative + false positive (Last, Spasoff, Harris, Thuriaux, & International Epidemiological Association., 2001)

***Total error*** is calculated using the coefficient of variation and laboratory bias (accuracy) [Total Error= % Bias + 1.96 (Coefficient of Variation)] (Bachorik & Ross, 1995). Thresholds are established for the degree of acceptable total error that meets national standards. Because no test is perfect, a certain amount of error is expected, with the goal of minimizing it as much as possible.

***Validity*** of a tool is a method of assessing whether a tool is measuring the construct it is supposed to measure; validity cannot be established in a tool that is not reliable (Nunnally & Bernstein, 1994). Several sources of validity can be achieved, including content validity, criterion validity and construct validity (Switzer, Wisniewski, Belle, Dew, & Schultz, 1999)

## Chapter 5

### Introduction

Coronary heart disease continues to be the leading cause of mortality in the United States (U.S.), resulting in a death every minute from a cardiac event (Thom et al., 2006). While rare in the military population, the impact of cardiovascular (CV) events in deployed military personnel pose a significant health threat. As the Global War on Terror (GWOT) approaches its 7th year, both U.S. active duty and reserve duty military personnel are "stretched and stressed" by continued and indefinite deployments overseas (On the readiness of the United States Army 2008). Occurrence of acute coronary syndrome (ACS) in a military force that must be healthy and physically capable to engage in physically demanding operational requirements is concerning. The U.S. military is regarded as young and physically fit, but as the senior ranks age, CV risk factors including dyslipidemia, hypertension, and subclinical atherosclerosis are common, even in presumably healthy, asymptomatic individuals (Hunt, O'Malley, Feuerstein, & Taylor, 2003). Military members also have extraordinarily high rates of smoking when compared to the civilian population [32.2% (Bray et al., 2006) versus 21.6% (Centers for Disease Control and Prevention , 2005)], with smoking rates increasing during deployments (Boos & Croft, 2004; DiNicola, Stanton, & Destfino, 2006). Smoking is a risk factor for CV events (Gehani et al., 2001), and acts synergistically with other CV risk factors, increasing the risk for ACS (Milionis et al., 2007). Predeployment health assessments do not address adequately CV risk, especially in older service members, and lack of timely preventive screening may contribute to the occurrence of ACS while overseas.

To date, one report of the prevalence of CV risk factors in military personnel deployed in support of the GWOT has been published. It was limited by the inclusion of 86% of the sample with no identifiable CV disease (CVD) (Sullenberger & Gentlesk, 2008). Reports of CV risk factor profiles exclusive to those service members deployed in support of GWOT with definitive CVD do not exist. The purpose of the current study was to identify and describe the prevalence of CV risk factors in military personnel with a diagnosis of ACS requiring invasive management who were deployed worldwide in support of the GWOT.

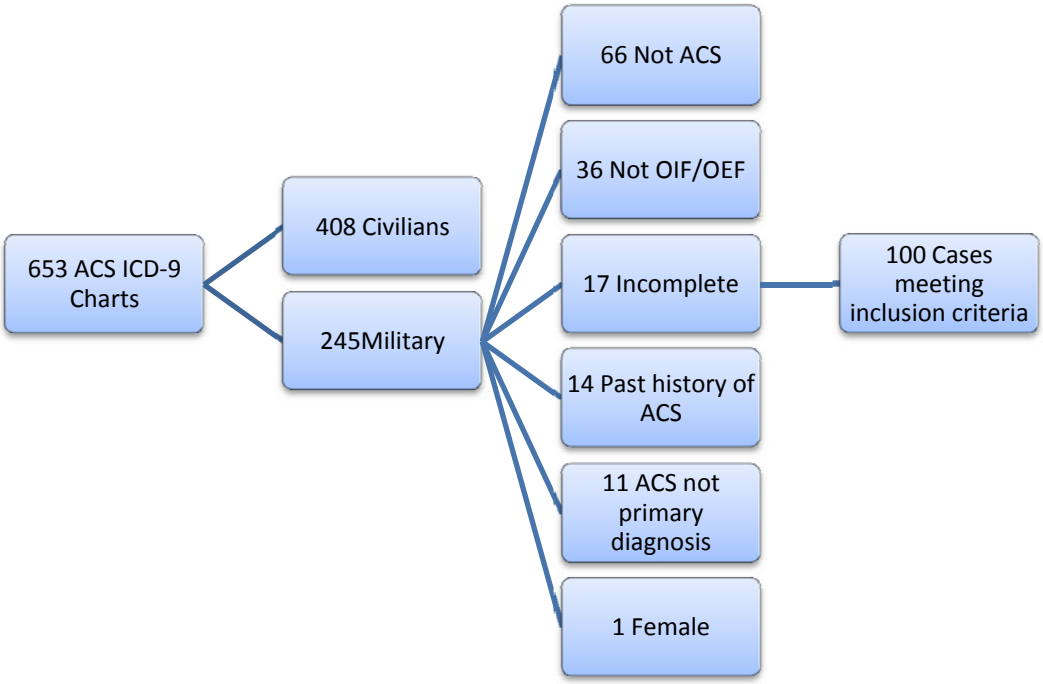
## Methods

The Institutional Review Boards at Walter Reed Army Medical Center, Washington, D.C., and the University of California, San Francisco approved this study.

### *Sample and Source of Data*

A retrospective chart review was conducted to obtain a sample of 100 male military members deployed overseas in support of the Operation Iraqi Freedom and Operation Enduring Freedom (OIF/OEF) who were treated at a major U.S. Army medical center in Germany between October 2001 and July 2007 with a primary diagnosis of ACS. ACS includes both acute myocardial infarction (AMI) and unstable angina. Cases of AMI included ST elevation MI, non-ST elevation MI with elevated troponin levels, and Q wave infarction. Administrators generated an initial query list of patients using the following three criteria: (1) International Classification of Disease-9 codes: 410.XX MI, acute; 411.1 angina, unstable; 413.9 angina pectoris, NOS; 427.5 cardiac arrest; or 414.01 coronary atherosclerosis, native coronary artery; 414.X, ischemic heart disease;

(2) prefix codes to the hospital identification number indicating the individual was a military service member; and (3) admission codes indicating the service member was deployed in support of OIF/OEF. Seven hundred four charts were identified for review. Investigators immediately eliminated 51 charts with a hospital identification code that identified them as other than a military service member. Six hundred fifty-three charts remained for further analysis of inclusion criteria (Figure 1).




ACS=Acute Coronary Syndrome; ICD-9=International Classification of Diseases-9; OIF/OEF=Operation Iraqi Freedom/Operation Enduring Freedom

**Figure 1 Records screened for inclusion in study**

A further 408 were identified as civilians. Omission of three variables from a chart rendered it incomplete and it was excluded from the study. Females were excluded from the study *a priori* since it was unlikely enough females experienced ACS to discuss substantively their risk factors. Consecutive chart review continued until investigators obtained 100 cases meeting inclusion criteria.

Investigators acquired clinical characteristics and cardiac risk factors using both hard copy and electronic records and reviewed progress notes from the initial site of patient presentation through admission and treatment at the medical center as available. Age, ethnicity, family history of premature coronary artery disease (CAD), and smoking history were recorded. If the family history was "unknown" or absent, patients were coded as having no family history of CAD (n=3). Individuals were considered "former smokers" if they quit more than 12 months prior to the CV event. An individual's past medical history of hypertension, dyslipidemia, and diabetes was annotated, along with the duration of diagnosis and any current pharmacologic treatment. Predeployment lipid values, fasting blood sugar, and blood pressures were collected if available. In cases where the patient denied dyslipidemia, but predeployment fasting laboratory values of total cholesterol $\geq$ 200 mg/dl, low density lipoprotein (LDL) cholesterol were $\geq$ 160 mg/dl or high density lipoprotein (HDL) cholesterol values were <40 mg/dl or triglycerides were $\geq$ 150 mg/dl , the patient's past medical history of dyslipidemia was changed to reflect a "corrected" history. No changes were made to self-reported medical history of hypertension because with the exception of severe hypertension, multiple measurements are necessary to make an accurate diagnosis (National Heart Lung and Blood Institute, 2003). Similarly, past medical history of diabetes remained unchanged because repeat laboratory testing on a different day is often required for diagnosis confirmation (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003). Investigators employed great effort to collect clinical data in a uniform manner. Systolic and diastolic blood pressures

obtained from the initial presentation for medical treatment of symptoms were used in the analysis. If unavailable, blood pressure measurements in closest proximity to the cardiac event were recorded. Total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides and blood sugar were typically obtained at the same time, and values recorded were those obtained at the medical center. A total cholesterol/HDL cholesterol ratio was calculated from these values. Investigators recorded measurements of height and weight from the cardiac catheterization record and used them to calculate body mass index (BMI) by dividing weight in kilograms by height in meters, squared ($kg/m^2$). If the catheterization record was unavailable, measurements were taken from other areas of the medical record. Framingham risk scores were calculated based on risk factor history and LDL cholesterol (Wilson et al., 1998).

*Statistical Analysis*

Data were analyzed using SPSS software (version 16.0). Descriptive statistics were used to characterize type of CV events, demographic characteristics and prevalence of risk factors. For continuous variables, means and standard deviations are presented; for dichotomous variables, frequency distributions are reported. In sub-analyses, Student's *t* test was used to compare means between groups and chi square analyses were conducted to compare dichotomous variables between groups.

## Results

The age range of this sample was 29 to 60 years, with 56% under the age of 45 years. Comparison of < 45 years and ≥ 45 years showed no significant differences between any major CV risk factors or past medical history, including individual lipid components and lipid ratio, glucose, blood pressure, smoking status, family history of premature CAD, or past medical history of hypertension or dyslipidemia (data not shown). Most of the sample had an AMI (82%); the remainder (18%) had unstable angina. The demographic and clinical characteristics of the sample are summarized in Table 1. Major CV risk factors were documented and Framingham risk scores calculated (Table 2). The prevalence of each individual risk factor is illustrated in Figure 2.

The total number of major risk factors for each individual was calculated using those identified by the NCEP/ATP III (2001): age ≥ 45 years, HDL cholesterol less than 40mg/dl, LDL cholesterol ≥ 160mg/dl, smoking history, blood pressure ≥ 140/≥ 90 mmHg or on anti-hypertension medications, family history of premature CAD in first degree family members and the CAD risk equivalent, diabetes. Eighty-eight percent of the sample had at least two CV risk factors; 58% had three or more risk factors; only 11% had one risk factor and 1% had no risk factors (Figure 3).

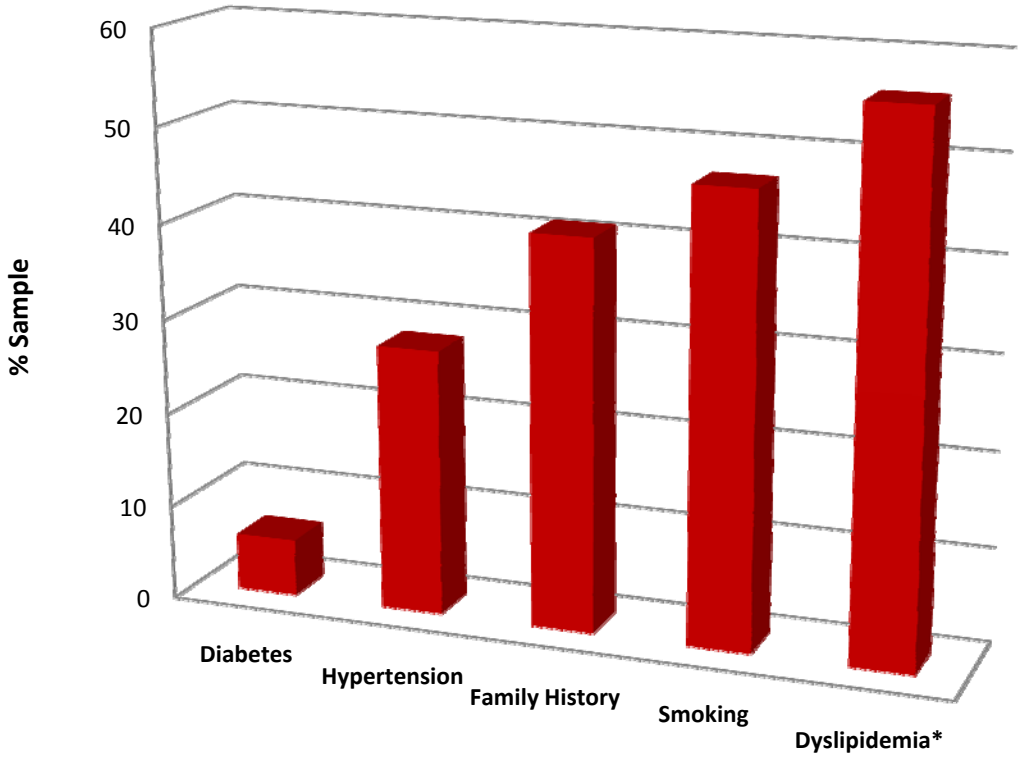
The most prevalent major risk factor was low HDL cholesterol (79%); the least prevalent was elevated LDL cholesterol (16%). The recorded values likely reflect the decrease that occurs in both values when drawn more than 24 hours after an AMI (Wattanasuwan, Khan, Gowda, Vasavada, & Sacchi, 2001); therefore the prevalence

| | Mean (sd) | % |
|---|---|---|
| **Age of total sample (years)** | 44.7 (7.8) | |
| **Active Duty** | 41.0 (7.4) | |
| **Reservists** | 47.2 (7.0) | |
| **Ethnicity** | | |
| **Caucasian** | | 76 |
| **African American** | | 14 |
| **Hispanic** | | 6 |
| **Asian** | | 2 |
| **Other** | | 2 |
| **Theater of operations** | | |
| **Iraq** | | 66 |
| **Afghanistan** | | 10 |
| **Other overseas GWOT location** | | 24 |
| **Branch** | | |
| **Army** | | 84 |
| **Air Force** | | 9 |
| **Navy** | | 5 |
| **Marines** | | 2 |
| **Status** | | |
| **Active Duty** | | 41 |
| **Reserve/National Guard** | | 59 |
| **Rank** | | |
| **Enlisted** | | 75 |
| **Officer** | | 25 |
| **History of hypertension** | | 28 |
| **History of dyslipidemia** | | 48 |
| **History of diabetes** | | 6 |

**Table 1 Patient Characteristics of Operation Iraqi Freedom/Operation Enduring Freedom acute coronary syndrome admissions (N=100)**

| | Mean (sd) | % |
|---|---|---|
| **Total Cholesterol (mg/dl)** | 177 (43) | |
| **LDL Cholesterol (mg/dl)** | 118 (41) | |
| **HDL Cholesterol (mg/dl)** | 35 (9) | |
| **Triglycerides (mg/dl)** | 149 (73) | |
| **Total Cholesterol/HDL Cholesterol ratio** | 5.3 (1.6) | |
| **Systolic Blood Pressure (mmHg)** | 125 (16) | |
| **Diastolic Blood Pressure (mmHg)** | 76 (12) | |
| **Glucose (mg/dl)** | 100 (30) | |
| **BMI (kg/m²)** | 27.77 (3.20) | |
| **≥ 30kg/m² (%)** | | 20 |
| **Family History CAD first degree relative** | | 41 |
| **Smoking** | | |
| **Never** | | 45 |
| **Current** | | 47 |
| **Former** | | 8 |
| **Framingham Risk Score** | 7.8 (4.4) | |
| **Low Risk (<10%)** | | 76 |
| **Intermediate Risk (10% to 19%)** | | 22 |
| **High Risk (≥ 20%)** | | 2 |

**Table 2 Cardiovascular risk factors of military men deployed in Operation Iraqi Freedom/Operation Enduring Freedom who experienced acute coronary syndrome (N=100)**




*Total cholesterol/HDL cholesterol ratio ≥ 5

**Figure 2 Risk factors of male military personnel with ACS deployed in the Global War on Terror (N=100)**

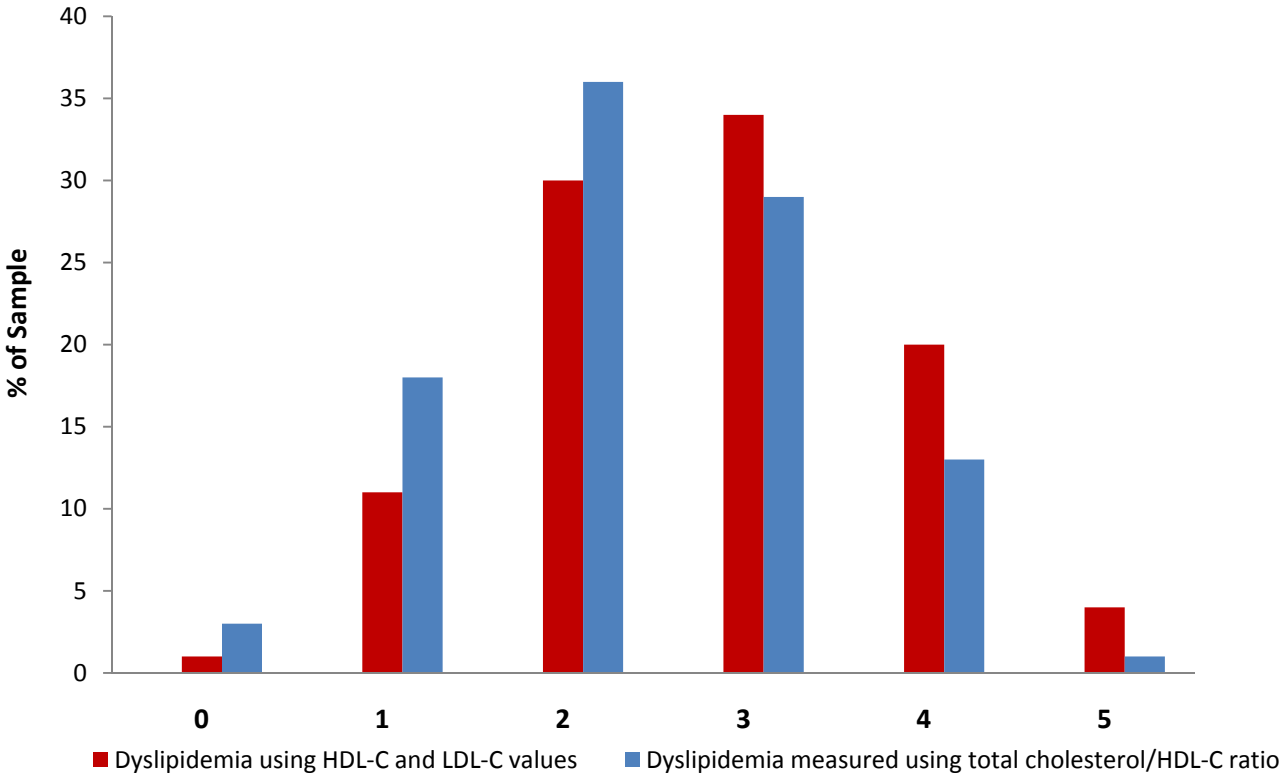
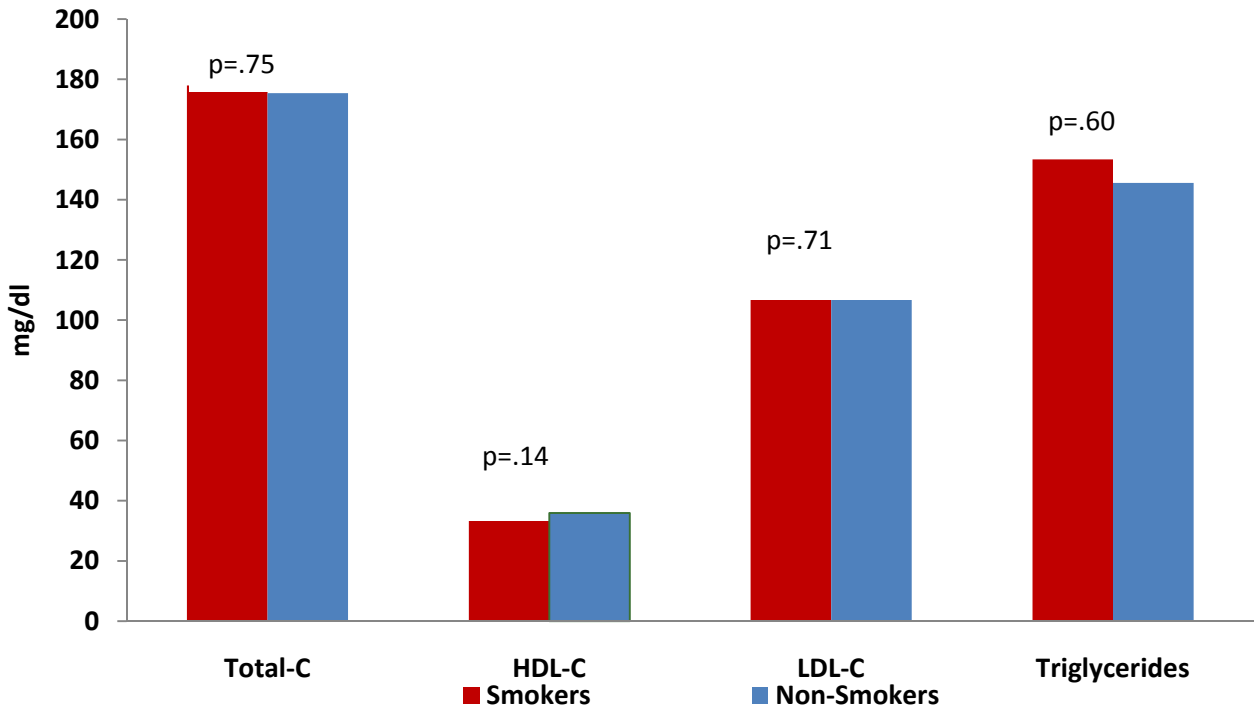



**Figure 3 Number of major CV risk factors in male military personnel with ACS deployed in the Global War on Terror (N=100)**

of low HDL cholesterol may have been overestimated and the prevalence of elevated LDL cholesterol underestimated. To minimize misclassification, we replaced LDL cholesterol and HDL cholesterol with a total cholesterol/HDL cholesterol ratio, with $\geq$ 5 as a measure of dyslipidemia. Those with 4 or more risk factors reduced from 24% to 14%; those with 0 or 1 risk factor increased from 13% to 24%. The substitution did not markedly affect those with 2 or 3 risk factors (Figure 3). Abnormal lipoprotein metabolism remained the most prevalent CV risk factor, with elevated total cholesterol/HDL cholesterol ratio present in 56% of the sample. A past history of diabetes was the least prevalent risk factor (6%). Hypertension was present in 40% of the sample, and while this finding should be interpreted with caution because of the

different time points at which the blood pressure was measured, it is consistent with the finding that of those with predeployment blood pressures (n=13), 46% had readings ≥140/≥ 90 mmHg or were taking anti-hypertension medications.

There is a known effect of smoking on lipoprotein metabolism (Ellison et al., 2004; Price et al., 1999), and a comparison of lipid profiles between current smokers versus never and former smokers was conducted. No significant differences were found between total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, or total cholesterol/HDL cholesterol ratio (Figure 4).




*Total Cholesterol/HDL Cholesterol Ratio: Smokers: 5.5; Non-smokers: 5.1

**Figure 4 Lipid profile comparison* between smokers (n=47) and non-smokers (n=53) in male military personnel with acute coronary syndrome deployed in the Global War on Terror**

Of this sample, 6% had serum glucose levels consistent with a diagnosis of diabetes mellitus, or $\geq$ 126 mg/dl; values suggestive of impaired fasting glucose (100-125 mg/dl) were identified in 22% of the sample.

Seventy-seven percent of the sample did not have documentation of predeployment lipid panels. Of the 23 individuals that had predeployment lipids recorded, 10 denied a history of dyslipidemia, however, all 10 had predeployment lipid panels consistent with abnormal lipoprotein metabolism.

## Discussion

The average age of military members across all services is 28 years; only 8.3% of the Army is over 40 years (Personal Communication, R.G. Dickinson, May 16, 2008). While younger age was expected based on the age demographics of all services, 70% of the sample was over the age of 40 years. This increased age of deployed men likely reflects the fact that over one-half of the subjects were reservists who were significantly older than the active duty personnel, but it also highlights the fact that older military personnel are deploying into combat environments. The mean age of the cohort, however, was similar to cohorts of active duty military personnel with CAD (43-45 years) (Barefoot et al., 1994; Ebersole, Miller, & Bailey, 1995; Osswald, Miles, Nixon, & Celio, 1996)

The overwhelming majority of service members deployed overseas in support of OIF/OEF treated at the medical center for ACS were “low risk” for a cardiac event according to their calculated Framingham risk scores. Given the mean age of the sample, this finding is not surprising. The Framingham risk score often underestimates CV risk in young people. For example, low Framingham risk scores were reported in an

analysis of cardiac deaths in a large civilian cohort of over 10,000 young men from the Chicago Heart Association Detection Project in Industry (Berry, Lloyd-Jones, Garside, & Greenland, 2007), and in other small observational studies of young AMI patients (Akosah, Schaper, Cogbill, & Schoenfeld, 2003; Sullenberger & Gentlesk, 2008; Zarich, Luciano, Hulford, & Abdullah, 2006). Most of the participants in this study had at least three major CV risk factors even when using total cholesterol/HDL cholesterol ratio as a measurement of dyslipidemia, implying that the Framingham risk score does not adequately capture global risk in military men with multiple CV risk factors. Framingham's absolute 10-year risk or relative risk may be misleading, lending support to advocates who suggest using lifetime risk to educate young men whose " low risk" is insufficient to motivate adoption of a therapeutic lifestyle (Lloyd-Jones et al., 2006). While the Framingham risk score has been validated in multiple populations (D'Agostino, Grundy, Sullivan, & Wilson, 2001), it considers neither lifestyle risk factors such as atherogenic diet, sedentary lifestyle and obesity, nor emerging risk factors, such as impaired fasting glucose, homocysteine, lipoprotein (a), proinflammatory factors, and measurements of subclinical atherosclerosis (NCEP/ATP III, 2001). While clinicians consider emerging risk factors along with Framingham risk scores to evaluate an individual's CV risk, expense and availability may preclude their use. Based on this study, it is unclear what additional risk factors would add predictive value to a service member's CV risk and this topic warrants further exploration. Family history is another important factor not used in the Framingham risk score calculation. Forty-one percent of subjects had a family history of premature CAD in first degree relatives and indeed,

evidence exists that family history independently predicts CV events in younger age groups (Milionis et al., 2007) and acts synergistically with traditional risk factors in CAD (Leander, Hallqvist, Reuterwall, Ahlbom, & de Faire, 2001).

Deployed service members are overweight based on BMI, a finding consistent with studies of young patients with AMI (Akosah, Cerniglia, Havlik, & Schaper, 2001; Akosah, Gower, Groon, Rooney, & Schaper, 2000). Twenty percent of the sample was obese based on a BMI greater than or equal to 30kg/$m^2$; in young men, BMI's at this level are associated with extensive atherosclerotic disease and vessel stenosis (McGill et al., 2002). It must be noted that BMI may not reflect accurately body fat in certain populations (Prentice & Jebb, 2001). It is unclear if the high BMI reflects increased body fat or an increasingly fit military force, whose muscular body composition falsely elevates BMI. While a recent study found use of BMI classification consistent with measures of body fat in Air Force men enrolled in a weight management program, generalizability to all military personnel may be limited (Heinrich et al., 2008). From a practical standpoint, the distinction in body composition is likely apparent to the clinician. If an elevated BMI reflects true adiposity, it must be considered in assessing an individual's risk (Grundy et al., 1998).

High density lipoprotein cholesterol confers protection from CV events and low levels of HDL cholesterol are identified in young patients who suffer an AMI (Zarich, Luciano, Hulford, & Abdullah, 2006). Due to the unique location of personnel deployed, HDL cholesterol values obtained in our sample were not collected in the critical 24-hour window of ACS presentation. Comparisons of the high prevalence of low HDL

cholesterol to other young ACS cohort studies are not valid because of the known reductions in lipid measurements after 24 hours of AMI. While the use of specific components of the lipid panel to assess CV risk is limited, the total cholesterol/HDL cholesterol ratio is a stable lipid parameter between acute illness and subsequent recovery of various illnesses (Nawaz et al., 2006). The ratio also remains constant between lipid panels obtained within 24 hours of an AMI and 4 days post AMI (Wattanasuwan, Khan, Gowda, Vasavada, & Sacchi, 2001). In large prospective studies, the total cholesterol/HDL cholesterol ratio predicts CV events as well or better than the individual components of lipid panels (Ingelsson et al., 2007; Lemieux et al., 2001).

Findings from The Quebec Cardiovascular Study (Lemieux et al., 2001) support associations between the atherogenic biomarkers of elevated total cholesterol/HDL cholesterol ratios and hyperinsulinemia, hypertriglyceridemia, small, dense LDL particles, and elevated apolipoprotein B, all indicative of the presence of insulin resistance. Over one quarter of the sample had glucose levels in the pre-diabetic or diabetic range, suggesting that insulin resistance may have been present in these individuals. Insulin resistance not only contributes to an individual's atherogenic lipid profile, but other CV risk factors are identified in the presence of hyperinsulinemia, including elevated blood pressure and increased thrombogenicity (Reaven, 1988). Evidence also exists that hyperinsulinemia independently predicts CV events (Despres et al., 1996).

Low HDL cholesterol would be an unexpected finding in deployed military men for several reasons; HDL cholesterol is largely influenced by physical activity (Kraus et

al., 2002) and vigorous exercise in service members is far greater than patterns seen in the civilian population [24.3% (Macera et al., 2005) versus 57.6% (Bray et al., 2006)]. Although the medical record rarely contained information on exercise patterns, it is likely that most deployed service members engaged in sufficient physical activity levels during operational requirements to increase their HDL cholesterol. Exercise has less effect on LDL concentration, but exercise decreases the number of small, dense LDL particles (Kraus et al., 2002). Conversely, the increase in smoking rates (Boos & Croft, 2004; DiNicola, Stanton, & Destfino, 2006) and the prohibition of alcohol consumption during deployment potentially affects optimal levels of HDL cholesterol (Ellison et al., 2004).

The findings of this study demonstrate the need to begin cholesterol screening at the age of 20 and every 5 years thereafter, in accordance with the NCEP/ATP III guidelines (2001), Army regulations are inconsistent with these recommendations, requiring a lipid panel only starting at age 35 in men and 40 in women (Army Regulation 40-501, 2007).

*Limitations*

The most significant limitation is the retrospective nature of the study and the variability of available data points. Acquisition of variable blood pressure data points may misclassify the presence of hypertension: lower blood pressures may reflect the initiation of pharmacologic management or changes that occur with bed rest; conversely, higher blood pressures may reflect acute anxiety at the initial presentation of the CV event. The prevalence of elevated blood pressure approximates rates

reported in active duty personnel (Andersen, 2004) but is slightly lower than the predeployment prevalence of elevated blood pressures in this sample. The individual components of a lipid panel cannot be assessed adequately, but use of the total cholesterol/HDL cholesterol ratio served as an adequate measurement of CV risk in these deployed service members. It was unclear, however, if the lipids and glucose samples were obtained in a fasting state. If they were not, the results of the both triglycerides and glucose may be spuriously elevated.

## Conclusion

This is the first study to identify and quantify major CV risk factors of U.S. service members deployed in wartime, all with a definitive diagnosis of ACS. Though the overall incidence of a CV event in a deployed service member is low, the occurrence of an event can have catastrophic effects on both the individual and the mission readiness of a forward deployed unit. The findings reported here raise two issues related to CV risk screening: (1) lipid panels prior to deployment were not documented in the majority of subjects, suggesting that military health care professionals are not following the NCEP/ATP III guidelines; and (2) a number of subjects with previously abnormal lipid profiles were unaware of their dyslipidemia. Screening in accordance with NCEP/ATP III guidelines must occur upon entry into the military and aggressive follow up and risk factor counseling and treatment is warranted for all individuals with dyslipidemia.

This study suggests that military members do indeed have heart disease and require counseling about smoking cessation, weight management, and management of dyslipidemia to minimize their risk for a CV event, especially prior to a stressful overseas

deployment. Further research is necessary to compare CV risk profiles with service members who deployed and did not experience a CV event. A low Framingham risk score clearly does not indicate “no risk”, and while it is the gold standard for assessment of global CV risk, future studies to examine additional biomarkers or risk factors yielding additional predictive value are necessary. Targeted intervention studies to address significant risk factors for CVD in this young population are critical to maintain a healthy, combat ready military force.

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# Chapter 6

## Introduction

After the terrorist attacks on September 11, 2001, the United States (U.S.) responded with military operations in Afghanistan in October 2001, followed in March 2003 with military action in Iraq. Today the U.S. government continues to deploy military personnel to conduct counterinsurgency and counterterrorism missions as part of the larger effort in the Global War on Terror (GWOT). Deployments are stressful for service members, particularly on personnel subject to extended deployments. The negative psychological effects of combat on deployed military personnel is well documented. Evidence supports the occurrence of acute cardiovascular (CV) events in deployed military personnel (Filardo et al., 2005; Sullenberger & Gentlesk, 2008); however, stress as a potential confounder of CV events has not been addressed.

Prior to deployment, both active and reserve service members undergo a medical screening process to ensure there are no medical conditions that would preclude deployment overseas. Adequate assessment relies on two components: disclosure of health problems by the service member followed by appropriate referrals by the clinician when warranted. Cardiovascular risk assessment is not part of the routine predeployment assessment; consequently, individuals with CV risk may go undetected. Sending service members overseas into combat with major CV risk factors creates a potentially catastrophic situation for both the individual and his or her assigned military unit. Besides traditional CV risk factors, the chronic stress of a

prolonged deployment that is punctuated by acutely stressful events, potentially place the service member at risk for developing acute coronary syndrome (ACS).

*Acute Stress Responses*

While knowledge of the physiology leading to CVD has evolved dramatically, there remain questions about the physiologic processes that occur with stress and their relationship to CV events. Theoretical models suggest that stress leads to the clinical consequences of myocardial ischemia, arrhythmias, thrombosis, and vulnerable plaque formation.(Rozanski, Blumenthal, & Kaplan, 1999) Indeed, stress exposure is associated with a number of physiologic changes, including increased heart rate (Ramachandruni et al., 2006) and blood pressure (Steptoe, Cropley, & Joekes, 1999), endothelial dysfunction (Spieker et al., 2002), arrhythmias (Culic, Silic, & Miric, 2005), increased platelet aggregation (Strike et al., 2006), and cardiac ischemia (Ramachandruni et al., 2006).

In studies of civilian cohorts both in and outside combat zones, ACS are associated with stress from a variety of sources ranging from home and work stress (Rosengren et al., 2004), to sudden missile attacks (Meisel et al., 1991) and other war related stressors (Sibai, Armenian, & Alam, 1991). Additionally, acute stress measured after the September 11th attacks followed by chronic worry related to terrorism was associated with increases in physician diagnosed heart problems (Holman et al., 2008). The deployments in support of the GWOT are stressful for military personnel. Though much of the public focus is on deployments to Afghanistan and Iraq, the military has service personnel deployed worldwide supporting or directly conducting

counterterrorism and counterinsurgency missions. It is likely that the specific area of deployment affects the level of combat stress experienced while overseas. Compared to other areas in the GWOT, Hoge and colleagues (2006) report increased psychological sequelae in combat veterans from Iraq and Afghanistan.

*Socioeconomic Status and Cardiovascular Disease*

Lower income and educational levels are associated with higher risk for coronary heart

disease in men (Eaker, Sullivan, Kelly-Hayes, D'Agostino, & Benjamin, 2004). Lower SES is associated with poor dietary intake, decreased physical conditioning, smoking, depression, hostility (Lynch, Kaplan, & Salonen, 1997), and access to healthcare (Lasser, Himmelstein, & Woolhandler, 2006). Higher perceived stress is also linked to individuals with lower income and educational levels (Rosengren et al., 2004).

In the military, rank is a surrogate measure of SES. Both income and education are related directly to military rank, and generally, those in the officer ranks have both higher income (Military Pay Tables, 2008) and higher education levels (Maxfield, 2005) than enlisted ranks. Although the architecture of the military health care system calls for equal access to care for officers and enlisted personnel, enlisted military members still have poorer health outcomes when compared to officers (Paris, Bedno, Krauss, Keep, & Rubertone, 2001; Tarman et al., 2000). Additionally, enlisted personnel report greater stress and anxiety during deployment than officers (McNulty, 2005).

The purpose of this study was to compare traditional CV risk factors between military personnel who deployed overseas in support of the GWOT and experienced ACS and those who deployed overseas in support of the GWOT and did not experience ACS.

## Methods

The Institutional Review Boards at Walter Reed Army Medical Center, Washington, D.C., Madigan Army Medical Center, Tacoma, Washington, and the University of California, San Francisco, San Francisco, California approved this study.

### *Sample*

This case control study is comprised of 93 cases with ACS and 1 to 3 matched healthy controls for every case (n=136). In an attempt to minimize the effects of SES, stress, and well-documented differences in heart disease between ethnic groups (Budoff et al., 2006; Rosamond et al., 2008; Shaw et al., 2008), cases were matched with controls of similar rank (officer ranks, enlisted ranks), area of operations (Iraq/Afghanistan, other GWOT location) and ethnicity (Caucasian, African American, other). Age was not a matching factor because it was controlled in the multivariable analysis.

Inclusion criteria for participants in the study included male gender, active duty, reserve or National Guard military members of any service deployed overseas in the GWOT, and no known history of coronary artery disease (CAD). Individuals were excluded if they were missing three or more variables of interest.

*Cases.* The cases were obtained from a query list at a military medical center in Europe. All patients with an International Classification of Disease-9 code identifying the individual as a service member deployed in the GWOT treated at the facility for ACS

between October 2001 and July 2007. Cases met inclusion criteria and had a primary diagnosis of ACS. Evaluation of information in the medical record confirmed that the subject met the eligibility criteria.

*Controls.* Controls were recruited through placement of posters in medical clinics servicing military personnel at a large military installation in the Pacific Northwest. Additionally, service members returning from an overseas deployment were provided with information on the research study by the primary investigator at their redeployment briefings.

*Data Collection*

A record review was conducted using electronic records and medical records. Information on age, ethnicity, branch of service and duty status (active or reserve), and family history of premature CAD in first-degree family members as well as personal history of hypertension, diabetes or impaired fasting blood sugar, and dyslipidemia was annotated. If no history of dyslipidemia was reported, but predeployment values revealed a high-density lipoprotein (HDL) cholesterol < 40 mg/dl, low-density lipoprotein (LDL) cholesterol $\geq$ 160 mg/dl or triglycerides $\geq$ 150 mg/dl, an additional variable of "corrected" history of dyslipidemia was created to reflect the actual history of dyslipidemia. Predeployment glucose, blood pressure, height and weight were also obtained as available. Individuals were classified as former smokers if they had not smoked in the past 12 months. If a participant smoked any form of tobacco, including pipes and cigars in the previous 12 months, they were categorized as smokers. Framingham risk scores were calculated on all participants using age, LDL cholesterol,

HDL cholesterol, systolic and diastolic blood pressure, presence of diabetes, and smoking status (Wilson et al., 1998). To measure dyslipidemia, a total cholesterol/HDL cholesterol ratio was calculated. For ACS cases, blood pressure, lipid panel, blood sugar, height and weight were the first ones obtained after the CV event.

In addition to the record review, a face-to-face interview and assessment of the following clinical characteristics were obtained on all the controls.

*Blood pressure.* Blood pressure was obtained with the patient seated using a Baum® aneroid sphygmomanometer and appropriate sized cuff. The participant's arm was bare and at heart level. Two blood pressures were taken, with the average recorded for analysis.

*Anthropometric measurements.* Height and weight were measured on a Detecto® manual physician scale with height rod. Height was measured without shoes to the nearest 0.25 inch and weight was measured in the lightweight army combat uniform with pockets emptied and without boots to the nearest 0.25 pound.

*Lipid profile and fasting blood sugar.* After an overnight fast, participants returned for a venous blood draw. Approximately 5 ml of blood were drawn in a Vacutainer® with serum separator. Blood was centrifuged for 20 minutes and serum was extracted and stored in cryovials at -70 degrees Fahrenheit until shipment to a central laboratory. Lipid measurements were measured using the Vertical Auto Profile test (Atherotech, Birmingham, Alabama), and residual venous blood was used to determine fasting blood sugar using an Ascensia Contour® glucometer (Bayer Healthcare, Tarrytown, New York). Using venous blood, the Contour® has an acceptable coefficient of variation of 4.2%.

Accuracy is demonstrated using an error grid analysis with 97.9% of specimens falling within zone A, or ± 15% or ± 10 mg within the laboratory measurements. Quality control checks were conducted routinely.

Statistical Methods

Data were analyzed using SPSS software (version 16.0). Chi square analyses were used to assess differences in the categorical matching factors. Student's *t* tests were used to assess differences of continuous variables between cases and controls; chi square analyses were used to evaluate differences between dichotomous variables. Univariate conditional logistic regression models were used to determine significance of individual risk factors with the outcome of ACS. Independent variables with $p < .20$ were entered into the conditional logistic multivariate analysis.

## Results

Ninety-three cases and 137 SES, stress, and ethnicity-matched controls were used in the analysis.

No statistically significant differences were found between cases and controls on the matched characteristics (Table 1).

Of the 93 cases, 81.7% were diagnosed with AMI and 18.3% with unstable angina. The mean age of cases was 44.6 years (± 7.8), with a range of 29 to 60 years, and nearly three quarters were enlisted personnel. Both groups have a mean BMI in the overweight category. More specifically, 62.4% and 52.6% of cases and controls, respectively, were overweight, with a BMI between 25 and 29.99 kg/m². A BMI of 30 kg/m² was recorded in 20.4% of cases and 36.8% of controls. The mean fasting blood

sugar was over 100 mg/dl in both groups; the range in the healthy controls was 64 to 133 mg/dl and in the ACS cases, it was 77 to 300 mg/dl.

| | Cases | Controls | p |
|---|---|---|---|
| **Rank (%)*** | | | |
| **Officer** | 25.8 | 26.5 | NS |
| **Enlisted** | 74.2 | 73.5 | NS |
| **Area of Operations (%)*** | | | |
| **Iraq or Afghanistan** | 82.8 | 86.8 | NS |
| **Other Global War on Terror location** | 17.2 | 13.2 | NS |
| **Ethnicity (%)** | | | |
| **Caucasian** | 78.5 | 74.3 | NS |
| **African American** | 15.1 | 16.9 | NS |
| **Other** | 6.5 | 8.8 | NS |

*Rank=SES, Area of operations=stress

**Table 1 Comparison of Matching Factors between Cases and Controls (N=229)**

After controlling for SES, stress, and ethnicity, most major CV risk factors were significantly different between the two groups with the exception of blood sugar and history of dyslipidemia (Table 2). In a univariate conditional logistic regression analysis, all CV risk factors except blood sugar were significant predictors of ACS (Table 3).

| | Cases | Controls | p |
|---|---|---|---|
| **Age (years)** | 44.6 (7.8) | 38.5 (5.5) | <.001 |
| **Total Cholesterol/HDL Cholesterol ratio** | 5.29 (1.57) | 4.18 (.95) | .001 |
| **Blood sugar (mg/dl)** | 100 (31) | 100 (13) | .925 |
| **Body Mass Index (kg/m²)** | 27.80 (3.23) | 28.92 (3.26) | .009 |
| **Framingham Risk Score (%)** | 7.55 (4.22) | 4.51 (2.37) | <.001 |
| **Family History of Premature CAD (%)** | 43.0 | 11.8 | <.001 |
| **Current Smoker (%)** | 45.2 | 29.4 | .015 |
| **History of Hypertension (%)** | 28.0 | 13.2 | .005 |
| **History of Dyslipidemia (%)** | 47.3 | 40.4 | .303 |
| **History of Diabetes/Impaired Fasting Glucose (%)** | 5.4 | 0.7 | .031 |

*Mean and SD shown for continuous variables; frequencies shown for dichotomous variables

**Table 2 Comparison of Clinical and Demographic Characteristics between Cases (n=93) and Controls (n=136)***

In a multivariate analysis where the criteria for significance was $p < .05$, higher age, higher total cholesterol/HDL cholesterol ratio, and family history of premature CAD remained significant independent predictors of ACS in service personnel deployed overseas in the GWOT (Table 4). Considered by itself, smoking was significantly associated with ACS ($p=0.015$), however, it did not demonstrate a significant, unique contribution to prediction of ACS when evaluated along with the other five variables in the model. Smoking was tested with each of the individual variables to assess for

interactions, with none found. Only when the total cholesterol/HDL cholesterol ratio variable was removed from the analysis did smoking become significant.

| | OR (95% CI) | p |
|---|---|---|
| **Age (years)** | 1.21 (1.12, 1.30) | <.001 |
| **Total Cholesterol/HDL Cholesterol ratio** | 2.33 (1.66, 3.26) | <.001 |
| **Blood sugar (mg/dl)** | 1.00 (.99,1.01) | .881 |
| **Family History of Premature CAD** | 4.43 (2.25, 8.75) | <.001 |
| **Current Smoker** | 2.27 (1.15, 4.30) | .015 |
| **History of Hypertension** | 3.01 (1.41, 6.40) | .004 |
| **Body Mass Index ($kg/m^2$)** | .89 (.81, .97) | .012 |
| **Framingham Risk Score (%)** | 1.36 (1.20, 1.53) | <.001 |

**Table 3 Univariate Conditional Logistic Regression of CV risk factors in Military Personnel Deployed in the Global War on Terror (N=229)**

| | OR (95% CI) | p |
|---|---|---|
| **Age** | 1.24 (1.11, 1.39) | <.001 |
| **Total Cholesterol/HDL Cholesterol ratio** | 2.85 (1.65, 4.93) | <.001 |
| **Family History of Premature CAD** | 4.83 (1.66, 14.65) | .004 |
| **Current Smoker** | 2.19 (.70, 6.44) | .182 |
| **History of Hypertension** | 2.68 (.85, 8.47) | .090 |
| **Body Mass Index** | .87 (.75, 1.02) | .093 |

**Table 4 Multivariate Conditional Logistic Regression Model of CV risk factors in Military Personnel Deployed in the Global War on Terror (N=229)**

## Discussion

Increasing age, family history of premature CAD, and dyslipidemia independently predict the occurrence of ACS in military personnel deployed in support of the GWOT. While findings of increased age as a risk factor for CVD was expected, the mean age and age range of the group was still very young. This finding has implications for ongoing health care costs, disability, possible separation from the service, and mortality. The health care costs for ongoing follow up care as well as the disability assessed after separation from the service can be significant. Furthermore, a unique aspect of the military profession is that the physical health of an individual can potentially affect career progression. Individuals diagnosed with an AMI must successfully complete a 120-day trial of duty to remain on active duty; if unsuccessful, a medical board may convene to determine eligibility for continued service. Finally, while young patients with AMI generally have better short term health outcomes than older patients with AMI (Anderson et al., 2008), evidence suggests high long term mortality rates in young AMI patients (Cole, Miller, Sperling, & Weintraub, 2003).

Despite the significant difference between groups on their Framingham risk scores, both groups were "low risk" or less than 10%. A significant limitation of the Framingham risk score (Wilson et al., 1998) is that it does not include family history in the algorithm, and given its independent association with ACS in this study, this omission cannot be ignored when evaluating CV risk in young military personnel. Evidence exists that family history of cardiac disease independently predicts CV events (Eaton et al., 1996) and may act synergistically with traditional risk factors in CAD

(Leander, Hallqvist, Reuterwall, Ahlbom, & de Faire, 2001). In young men, family history is shown to be particularly important. Young AMI patients (less than 35-45 years) have significantly higher rates of premature CAD in family members when compared to older AMI patients (Pineda et al., 2008; Zimmerman, Cameron, Fisher, & Ng, 1995). The risk factor profile of patients with and without a family history of premature CAD is different. Patients with a family history are male, younger, and have a greater prevalence of smoking and dyslipidemia when compared to patients without a family history of premature CAD (Harpaz, Behar, Rozenman, Boyko, & Gottlieb, 2004). Seeking additional biomarkers or risk factors that add predictive value to the Framingham risk score must be sought for young military personnel. The new physical health assessment addresses family history as a key component, something that was missing from previous physical exam forms. The addition is a positive step and is likely to identify those who may be at higher risk for CVD, but whose Framingham risk score is low.

Historically, military personnel were required to have a physical examination every 5 years and lipid panels were not assessed in service members under the age of 40; rather, only a total cholesterol was required. A "low" total cholesterol may be the result of a low HDL cholesterol and give a false sense of wellness when in fact this is a risk factor that warrants counseling at a minimum, and depending on other risk factors, pharmacologic management. Recently the Army improved their health surveillance program, transitioning from the periodic 5-year comprehensive physical examination to an annual physical health assessment. Assessment of lipid panels in the new system, however, are not required until age 35 in men and 40 in women, which is inconsistent

with the American Heart Association (Pearson et al., 2002) and NCEP/ATP III guidelines ("Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection Evaluation And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III)", 2001) that recommend complete lipid panels every 5 years beginning at age 20.

One-half of the entire sample had no evidence of previous lipid testing in their records. Lack of CV risk prevention may be a result of the transient nature of the military population; it could also be argued that unavailability of reservist's civilian medical record overestimates this percentage. With the military's dependence on reservists to maintain the current deployment schedule, however, it is imperative for military health care providers to know the current lipid panel of activated reservists. If none can be produced, the lipid panel must be duplicated. The independent association of total cholesterol/HDL cholesterol ratio with ACS is consistent with findings in large prospective studies (Ingelsson et al., 2007; Lemieux et al., 2001), and higher ratios are associated with features consistent with insulin resistance, including hyperinsulinemia, small, dense LDL particles, and elevated apolipoprotein B, the structurally important component of VLDL, IDL, and LDL (Lemieux et al., 2001). Even use of direct measures to quantify insulin resistance suggests that individuals with higher lipid ratios are indeed insulin resistant. It is unclear, however, whether the increased risk for ACS is related to abnormal lipoprotein metabolism, or the association of lipid ratios with hyperinsulinemia and glucose intolerance (Jeppesen, Facchini, & Reaven, 1998). Early screening is essential, and health care providers must assess the number of CV risk

factors of service members, irrespective of age. Global risk assessment must happen during their annual physical health assessment and most importantly, prior to an overseas deployment.

The lack of association of smoking to CV events in this sample was unexpected. Although smokers deployed in support of the GWOT were twice as likely to have ACS, the effect was not large enough to be statistically significant. The findings do not to suggest that smoking is not a risk factor for CV events, as smoking is unequivocally associated with increases in CVD. Smoking stimulates sympathetic nervous system activity and increases an individual's thrombogenicity (Viles-Gonzalez, Fuster, & Badimon, 2006), potentially predisposing a vulnerable person to ACS. Additionally, smoking is sometimes noted as the only CV risk factor associated with the occurrence of AMI in young patients (Gehani et al., 2001). In civilian cohorts of young patients with AMI's, however, rates of smoking are reported at 74% or higher (Anderson et al., 2008; Doughty et al., 2002), considerably greater than the reported prevalence in our cases of 45%; also the insignificant findings indirectly highlight the high rates of smoking in the control group. A larger sample size would likely detect differences between the groups. Alternatively, evidence suggests that not all smokers are at equal risk for development of an atherogenic lipid profile. Insulin resistant smokers have significantly different lipid profiles than insulin sensitive smokers, including small, dense LDL particles, hypertriglyceridemia, and increased VLDL cholesterol (Farin et al., 2007). Furthermore, ACS outcome studies suggest similar findings. In the Copenhagen Male Study, (Jeppesen, Hein, Suadicani, & Gyntelberg, 2001) found no differences in the incidence of

ACS between non-smokers with low HDL cholesterol-high triglyceride dyslipidemia and smokers with a high HDL cholesterol-low triglyceride pattern.

The prevalence of smokers in the control group was much lower than the reported rates of smoking in the general military (32.2%), and specifically Army personnel (38.2%); irrespective of case or control group, however, the smoking rate in this sample of military personnel exceeded the overall prevalence in the civilian population (22.1%) (Centers for Disease Control and Prevention [CDC], 2005). Implementation of convenient and accessible smoking cessation programs is essential and should be offered every time the service member interacts with a health care provider to include predeployment, post deployment, at the mandatory 90-day redeployment assessment, and any health care visit.

While BMI was significant in the univariate analysis and trended towards significance in the multivariate analysis, it is important to address the inverse association that is not only counterintuitive but stands in contrast to a large population study with data supporting increased CV death with increased BMI (Calle, Thun, Petrelli, Rodriguez, & Heath, 1999). An argument could be made that the higher BMI in the healthy control group may reflect a conditioned, physically fit population versus a greater BMI attributable to higher abdominal adiposity. However, similar findings of BMIs greater than 25 $kg/m^2$ associated with increased CV mortality were also noted in a young cohort of construction workers who are physically active (Arndt, Rothenbacher, Zschenderlein, Schuberth, & Brenner, 2007). With military personnel, it is unclear whether BMI reflects increased lean muscle mass or true adiposity and the use of BMI

to appraise health risks may not be valid in the military population. Other correlates of obesity, such as measurements of body fat or waist circumference, warrant further exploration in this population. This should not diminish the fact that both groups are indeed overweight, or that nearly one-third of the entire sample was classified as obese with a BMI $\geq$ 30 kg/m$^2$. Young men who are obese based on BMI have significant atherosclerotic disease with vessel stenosis (McGill et al., 2002).

Finally, though no differences were noted between groups with respect to fasting blood glucose, the mean of both groups was greater than 100 mg/dl, meeting criteria for impaired fasting glucose. Individuals with impaired fasting glucose are not necessarily insulin resistant, however, (Kim & Reaven, 2008) report insulin resistance in 57% of individuals with impaired fasting glucose. Additionally, those with impaired fasting glucose had a higher BMI, systolic and diastolic blood pressure, lower HDL cholesterol, and higher triglycerides when compared to individuals with normal glucose tolerance and consequently are at greater CV risk.

The case-control design is useful to study infrequent outcomes or disease processes that develop over extended periods of time (Grimes & Schulz, 2002). It was optimal to study CVD in military personnel because not only is ACS relatively rare in the military, but CVD is a pathophysiologic process that develops over many years, making cross-sectional and longitudinal studies inappropriate in this low risk population. This study was especially strong because there was matching of rank, area of operation, surrogate measures of SES and stress, respectively, and ethnicity.

*Limitations*

Ideally, in a case control study, the controls should be randomly selected to be a valid comparison group. Because this study required current clinical and laboratory measurements post deployment, random selection was not feasible. The retrospective nature of data collection in the case group after the CV event is a limitation. Although problematic, the lack of timely laboratory results is somewhat mitigated by the stability of the total cholesterol/HDL cholesterol ratio (Nawaz et al., 2006; Wattanasuwan, Khan, Gowda, Vasavada, & Sacchi, 2001). Known inaccuracies of self-report of smoking history (Caraballo, Giovino, Pechacek, & Mowery, 2001; Payne & Southern, 2006) or family history of CAD (Bensen et al., 1999) may underestimate their true prevalence.

Direct comparisons of lab values obtained using different methods of measurement also pose potential weaknesses in this study. All controls had direct measurements of their lipid panels versus cases, where the LDL cholesterol was calculated using the Friedwald equation prior to October 2005. To improve precision and accuracy, the laboratory conducting lipid panels for the cases changed their protocol to direct measurement of LDL cholesterol in October 2005 (personal communication, Aziz Qabar, March 4, 2008). The calculated Framingham risk scores in this study are somewhat limited both by the use of calculated LDL cholesterol values that tend to be lower than the actual LDL cholesterol value and by the use of lipid panels that were obtained after an AMI. For these reasons, the true Framingham risk score may be underestimated in the cases.

Assessment of blood sugar using whole venous blood and a portable glucometer may have produced inaccurate measurements. The Ascensia Contour® meets the American Diabetic Association recommendations of 5% coefficient of variation, but exceeds the recommendations for total variability of < 10% ("Consensus statement on self-monitoring of blood glucose", 1987). Further research is needed to determine whether the results reflect changes in an individual's insulin sensitivity, inadequate fasting, or the accuracy of the glucometer.

## Conclusions

In summary, the most significant risk factors of ACS in deployed military personnel are age, family history of premature CAD and dyslipidemia. The military is presently engaged in a conflict with no foreseeable end, and preserving the health of military members is critical to maintain the current operational tempo. Seasoned enlisted personnel and officers are irreplaceable; the time and cost to produce these national assets is formidable. Improvement in preventive medicine surveillance programs may lead to greater numbers of service personnel having appropriate CV risk screening and intervention. The military must require its service members to use preventive health care services on a routine basis and ensure there are no barriers or stigma associated with health care utilization. The U.S. military makes every effort to ensure service personnel are capable of undertaking complex missions through extensive training and use of proper, functional equipment; the government is obliged to apply similar standards to ensure the cardiac fitness of every service member, especially those who are deployed in the GWOT.

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## Chapter 7

### Summary

The overall aim of this dissertation was to identify cardiovascular (CV) risk factors in military personnel deployed in the ongoing Global War on Terror (GWOT). The first data based paper from this dissertation gives evidence to support that military members do indeed have acute coronary syndromes (ACS) while deployed. The prevalence rates of smoking, dyslipidemia, and obesity suggest that counseling about prevention and/or management of these risk factors may minimize the risk for ACS in deployed service members. The second data based paper was a case-control study that compared CV risk profiles between service members who deployed in the GWOT and experienced ACS and service members who deployed in the GWOT and did not experience ACS. Despite controlling for socioeconomic status (SES), stress, and ethnicity, several major CV risk factors remained significant in the multivariate analysis. Risk factors that independently predicted ACS in deployed military personnel were age, family history of premature coronary artery disease (CAD), and dyslipidemia.

One of the most enlightening findings in both papers is that in both ACS and healthy control groups, the mean Framingham risk score was “low risk”, or less than 10%. The papers suggest that “low risk” is not equivalent to “no risk” and clearly illustrates that though the Framingham risk score is the gold standard for assessment of global CV risk, this simple scoring tool may not adequately predict risk in young military personnel. Accurate CV risk assessment and prevention are often overlooked in a young population, but they are critical to maintain a healthy, combat-ready military force. Until better measures of global CV risk in young military personnel are determined,

however, the absolute number of CV risk factors and routine calculation of Framingham risk scores must be assessed yearly, but most importantly, prior to an overseas deployment. Cardiovascular disease has a multifactorial etiology, however, the findings from this dissertation have pertinent implications at several levels within the Department of Defense hierarchy, including clinical implications for military personnel and health care providers, theoretical implications that warrant further exploration, and service-wide policy implications. Additionally, this study also serves as a catalyst for future studies to examine CV risk in our nation's military. Much work is still needed from a preventive medicine standpoint to provide first-rate care for our military service members—for *my guys*.

*Clinical Implications*

*Smoking Cessation* Smoking is unequivocally associated with increased CVD. Clinicians must assist with a concerted effort to eliminate smoking in military personnel whether living in the United States or deployed overseas. It is difficult to obtain pharmacological treatment due to the mandatory requirements to attend smoking cessation groups. Military personnel are reluctant to admit any physical or psychological deficit or dependency; requirements for attendance in a group format is likely not appealing and may deter people who wish to quit from seeking care. Despite this, providers must still ask smokers if they have a desire to quit at both deployment related interfaces and any health care visit; "buy in" from the patient will occur only if smoking cessation guidelines are convenient for the patient.

*Cholesterol* The findings in this dissertation raise two important issues related to lipid screening in military personnel. First, lipid panels prior to deployment were not documented in the medical record in the majority of subjects, suggesting that military health care professionals may not be following the NCEP/ATP III (2001) or AHA guidelines (Pearson et al., 2002) for lipid screening; second, many subjects with previously abnormal lipid profiles were unaware of their dyslipidemia. Irrespective of military regulation, health care providers must act in the best interests of the patients ensuring each one has a current lipid profile and employ aggressive CV risk reduction measures with appropriate treatment and follow-up as necessary for individuals with dyslipidemia.

*Obesity* Higher BMI in the healthy control group may indicate a conditioned, physically fit population, but it is unclear whether this is true or if the greater BMI is attributable to greater adiposity. Sedentary lifestyle and unhealthy diet are significant risk factors that contribute to the prevalence of the obesity epidemic (Institute of Medicine, 2003). Working under the premise that the higher BMI is indeed related to increased adiposity, combating sedentary lifestyle in a culture immersed in computers, video games, and television is difficult; additionally, the emergence of "super size" portions allows individuals to consume calories far exceeding their needs. These cultural and social norms are often companions of a 17 or 18 year-old military recruit, and while the lifestyle in the military promotes physical activity, changing established behaviors is challenging and upward trends of obesity in the military are not surprising. Co-morbid conditions of overweight and obesity include hypertension, dyslipidemia,

diabetes, CVD, sleep apnea, and various cancers (National Heart Lung and Blood Institute, 1998). Military personnel are required to maintain height and weight standards for continued service, but health care providers still must provide education regarding the risks of ongoing overweight and obesity at every health care visit. This is especially important because the disease burden of obesity may affect a military career since some associated diseases are not compatible with military duties. Obesity alone or common chronic conditions relating to obesity may initiate a review of an individual's ability to carry out his or her military mission, and perhaps result in an administrative or medical separation from the service.

*Theoretical Implications*

The theoretical model as proposed in the introduction is not completely tested, largely because of the preponderance of missing GWOT Stress Scales in the ACS group (53%). When one ACS case is missing data, the entire "case-control family" is eliminated from the analysis. For this reason, analyzing the impact of traditional CV risk factor and minimizing the theoretical impact of stress and the known impact of SES and ethnicity on CVD was the most feasible way to use the most data.

The preliminary findings in a subset of cases and controls matched on age ($\pm$ 5 years) and ethnicity (N=105) suggest that after adjustment for age, family history of premature CAD, history of hypertension, dyslipidemia, smoking, and BMI, those with "high stress" as measured by the dichotomized GWOT Stress Scale score were more likely to experience ACS while deployed. The implication that stress is a risk factor for

ACS in deployed service members is consistent with finding in civilian observational studies and warrants further investigation.

*Military Implications*

While the Department of Defense and branches of the military bear some burden to minimize the implications of CVD, much of the responsibility is borne to the individual. While several CV risk factors are not modifiable, personal choices and personal responsibility to maintain ideal weight, engage in healthy eating and exercise patterns are paramount, especially in the presence of known risk factors that cannot be changed.

*Smoking* The harmful effects of smoking are well recognized, yet over 30% of military personnel continue to smoke, and this rate does not include those that use smokeless tobacco, which seems to have greater social acceptability. The exorbitant cost of cigarettes and the deleterious health effects of smokers and those they expose to second hand smoke should send a strong message of deterrence to military personnel for both for financial and health reasons; however, the smoking rates in the military remain high. One of many reasons given for smoking during deployment is stress (Boos & Croft, 2004; DiNicola, Stanton, & Destfino, 2006), an unfortunate fact that will not change, but implementation of stress management programs are ongoing in theater. The most sweeping policy is that smoking in military facilities is prohibited; "smoke breaks" are common and frequent among military personnel, suggesting a possible secondary gain to continue the habit. Cigarettes and smokeless tobacco are readily available and in the absence of a personal willingness to quit or an environment

that is conducive to quitting, it is unlikely that any policy reform will shift the rates of smoking in military.

*Cholesterol* Current military regulations do not support lipid testing until age 35 in men and 40 in women (AR 40-501, 2007). This is not in accordance with AHA (Pearson et al., 2002) or NCEP/ATP III (2001) recommendations. The independent association of total cholesterol/high density lipoprotein cholesterol ratio with ACS is consistent with findings in large civilian prospective studies (Ingelsson et al., 2007; Lemieux et al., 2001). The atherogenic lipid profile associated with higher ratios may go unnoticed for years if testing does not begin from the point of entry into the service and at regular intervals throughout a members' military career. Given the age range of ACS cases, this policy is unacceptable. While a service member can request lipid testing or a health care provider can order the test at other visits, this solution works under the assumption that the service member is aware that a lipid panel is needed at least every 5 years or that the health care provider ensures compliance with recommended guidelines. Given the fact that one-half of the sample had no evidence of previous lipid testing in their records, it is unlikely either is accomplished. Lack of CV risk prevention may occur for a number of reasons, including the transient nature of the military population, or perhaps increased demand for appointment availability and shortened appointment times preclude the health care provider's ability to engage in effective and comprehensive preventive medicine strategies.

The younger age groups experiencing ACS in the deployed military population has implications for ongoing health care costs, disability, possible separation from the

service, and mortality. Implementation of preventive health care strategies in the form of lipid and glucose screening will undoubtedly increase hospital-operating costs, however, recognition of dyslipidemia and treatment strategies would likely be a fraction of the costs associated with the astronomical costs for initial treatment and ongoing care and disability for a young AMI patient.

*Obesity* Large prospective studies show increased CV death with increased BMI (Arndt, Rothenbacher, Zschenderlein, Schuberth, & Brenner, 2007; Calle, Thun, Petrelli, Rodriguez, & Heath, 1999). The increased prevalence of illness within the overweight and obese population results in an enormous economic burden of their care, with costs continuing to rise (Elmer, Brown, Nichols, & Oster, 2004). The cost of hospital admissions and the economic implications for the military medical system related to the care of overweight and obese service members is tremendous: significant direct and indirect costs of obesity for active duty service members has been demonstrated in several retrospective studies (Bradham et al., 2001; Hoiberg & McNally, 1991; Robbins, Chao, Russ, & Fonseca, 2002)

Separation from the service due to obesity or obesity-related illness or disease has economic and military readiness effects. Individuals who leave the military with a critical skill can profoundly influence the military readiness of a service member's assigned unit and result in associated costs to the Department of Defense to move and/or train another soldier for replacement of the specific military skill qualification.

During the course of the study, both officer and enlisted personnel were critical of the military dining facilities while deployed, often lacking few healthy food choices.

One participant suggested changes to the military dining facility menus both in the United States and during deployment to provide healthier food choices would be of great benefit and implored me to take on the challenge. Finally, few military posts in the United States and overseas are without Burger King, Popeye's, and other fast food restaurants. Despite lack of nutritious menus, the accessibility and relatively low cost make these choices appealing, especially for enlisted personnel on a limited income.

*Future Studies*

*Alternative Biomarkers* The Framingham risk score poses limitations to assess CV risk in military personnel. Seeking additional biomarkers such as lipoprotein (a), low-density lipoprotein particle size, C-reactive protein, high-density lipoprotein sub-fractions or other risk factors that add predictive value to the Framingham risk score must be sought for young military personnel. New annual physical health assessment forms address family history as a key component, something missing from previous physical examination forms. The addition is a positive step, likely identifying individuals who are at higher risk for CVD, but whose Framingham risk score is low. Another area of exploration, however, is use of a different CV risk scoring tool to determine whether it stratifies risk better than the Framingham tool in military men.

*Body Mass Index* The higher BMI in the healthy control group is counterintuitive. Use of BMI to appraise health risks may not be valid in the military population, and other correlates of obesity, such as measurements of body fat or waist circumference, warrant further exploration in this population.

*Stress* War related stressors are associated with acute cardiac events in the

civilian population, but this area of research has been largely ignored for military personnel. An inherent difficulty of measuring stress in the military population is the stigma surrounding psychiatric disorders and traits. Expectations of strength and stoicism are pervasive throughout the military. Admission of weakness, especially mental weakness, is likely to be perceived negatively in this population. Additional studies that examine the relationship between acute and chronic stress during deployment and the occurrence of ACS must be conducted using reliable and valid stress measurement tools. Comparison of traditional CV risk factors and a stress measurement score using a case-control design with participants matched exactly on age, rank, and ethnicity as originally proposed would be useful. Rather than use of a proxy measurement of stress, validated tools administered during the hospitalization in Germany after evacuation from the area of operations would eliminate the problems with missing data that were difficult to overcome in this dissertation.

A repeated measures study would be optimal to assess the effects of the war on the CV risk profile of service members over the course of a 12-month deployment. In addition to stress measures, assessment of changes in major CV risk factors, as well as other biomarkers associated with CVD such as insulin resistance, C-reactive protein, plasminogen activator inhibitor, interleukin-6, tumor necrosis factor alpha, monocyte chemoattractant protein-1, intercellular adhesion molecule-1, vascular cell adhesion molecule-1, P-selectin, E-selectin, and lipoprotein associated phospholipase A2 would be of interest.

## Conclusion

The occurrence of a CV event can have catastrophic effects on both the individual and the mission readiness of a forward deployed unit. Based on post-mortem studies, it is known that the precursors to CVD begin in childhood. While difficult to change behaviors that are not conducive to CV health, the military establishment must lead by example by encouraging service members to quit smoking, providing heart healthy menus in the dining facilities at home and abroad, employing adequate physical fitness programs, and constant education on smoking cessation, weight management, and the effects of eating an unhealthy diet. Improvement in military preventive medicine surveillance programs may lead to greater numbers of service personnel identified with CV risk factors. While personal responsibility to engage in a healthy lifestyle cannot be ignored, pilot testing programs in military units for CV risk screening and CV health education can augment current knowledge and reinforce healthy lifestyle behaviors. Such programs are essential to ensure the maintain and improve the CV health of our Nation's most treasured assets, the young military service members who voluntarily serve in the Armed Forces to protect United States interests, often at the sacrifice of their own.

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