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Prevalence of Spurious Systolic Hypertension in an Active Young Adult Population

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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
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14. ABSTRACT

15. SUBJECT TERMS

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a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			Cory Hedin
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1. REPORT DATE. Full publication date, including day, month, if available. Must cite at least the year and be Year 2000 compliant, e.g. 30-06-1998; xx-06-1998; xx-xx-1998.

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DEPARTMENT OF THE AIR FORCE
60TH MEDICAL GROUP (AMC)

11 July 2018

MEMORANDUM FOR DR. SACHIN SHAH

FROM: 60 MDG/SGSE

SUBJECT: Expiration Notice for Research Protocol FDG20150026H

1. A recent audit of our research protocol files has indicated that your research protocol FDG20150026H, "Prevalence of Spurious Systolic Hypertension in an Active Young Adult Population" expired as of 12 June 2018.

2. The protocol office gave a 60 day notice and provided a template for the continuation report on 12 March 2018 as it was due to meet the May IRB meeting. A temporary suspension notice was sent from the compliance office on 19 June 2018.

3. Because a continuing review report was not submitted to the Institutional Review Board (IRB) prior to the expiration date in accordance with DoDI3216.02_AFI40-402, all research activities must stop immediately, and no new subjects may be enrolled. If it is in the patient's best interest to continue receiving care under the protocol, you must to file a statement as per SGSE OI 40-402-01 3.4.3

4. The IRB has officially administratively closed your study and your squadron commander will be notified of this action.

JAMES D. KISER, Colonel, USAF, DC
Chair, Institutional Review Board

PROPOSAL FOR HUMAN RESEARCH

CLINICAL INVESTIGATION FACILITY
60th Medical Group (AMC)
David Grant USAF Medical Center
101 Bodin Circle
Travis AFB, CA 94535-1800

FWA00003321, DoD 50004, IRB00002726

For assistance, call the Chief, Research Oversight and Compliance at (707) 423-7206

1. Title of Investigation

Prevalence of Spurious Systolic Hypertension in an Active Young Adult Population

2. Investigator and Investigation Staff

Name	Rank *	Study Role	Date of Investigator Training	Staff/ Resident/ Fellow **	Dept/ Office Symbol	Phone	DoD Assurance Number***	E-mail
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3. Facility and/or Contractor

David Grant Medical Center (DGMC), Travis AFB, CA

4. Purpose of Investigation

This investigation will do a prospective evaluation of preventative health assessment (PHA) records. The primary objective is to determine the prevalence of pseudo or Spurious Systolic Hypertension (SSH) in an active young adult population. This investigation will also compare the established normal brachial blood pressure (BP) ranges with central blood pressure (cPB) in an active young adult population. We will also describe the association between self-reported levels of physical activity and cBP parameters.

5. Category of Study and Risk Assessment

5.1. Category of Study

☐ **Medical Utilization** ☒ **Prevention** ☐ **Medical Readiness** ☒ **Diagnosis/Treatment/Other**

The proposed study has been put forward as minimal risk as all interventions are those encountered in daily life or experienced during a routine physical exam.

Further, the study team believes that the study is eligible for expedited review under category 5.

5. Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis).

The Web Health Assessment (Web HA) is performed by each active duty member annually during their preventative health assessment. All data pulls will be from the WebHA and data collected during the subject's annual PHA appointment

5.2. Proposed Risk:

☒ Minimal Risk
☐ Greater Than Minimal Risk

The collection of DGMC PHA clinic data has no additional risk above and beyond the risk of inadvertent disclosure of subject health information.

6. Proposed Research

6.1. Background and Review of Literature:

- **Disease Burden & Diagnosis:** Hypertension is the leading global risk for mortality[1] and is a major risk factor for future cardiovascular disease[2] that affects nearly one third of adults in the United States and costs $131 billion annually[3,4,5]. A plentitude of epidemiological data supports the observation that elevated blood pressure in asymptomatic individuals relates to future cardiovascular risk[6,7].

  Traditionally, hypertension is diagnosed and treated by assessing the pressure at the brachial artery (peripheral BP)[8]; however, recent evidence suggests central hemodynamics are better predictors of cardiovascular outcomes and mortality[9,10]. This is due to the fact that cBP is indicative of the pressure directly exerted on target organs[8], while peripheral BP is affected by amplification of blood pressure wave reflections caused by variance in arterial stiffness[8,9,10]. As a result of arterial stiffness increasing with distance from the heart, peripheral systolic blood pressure (SBP) is typically greater than central SBP[11]. Many factors affect arterial stiffness, including age and gender, leading to variations in the differences seen between peripheral BP and cBP[9,10]. This means that in

some individuals, a peripheral BP measurement may equate to a diagnosis of hypertension, while the cBP more accurately denotes normal values.

The body of evidence showing that cBP is a more accurate predictor of cardiovascular risk is continuing to grow. For example, in the CAFE Study central Pulse Pressure (PP), the difference between systolic and diastolic pressures, was shown to be related to cardiovascular risk.[12] Safar et al described that central PP was related to the risk of death in patients with renal insufficiency, but no such association could be shown for peripheral pressure.[13] Roman et al studied patients with risk factors but without symptoms of CAD and concluded that central aortic pressure better predicts incident cardiovascular disease than brachial pressure.[14] Wang et al demonstrated superior correlation between central SBP and left ventricular mass, carotid intima-media thickness, estimated glomerular filtration rate, and cardiovascular mortality.[15]

Until recently, the measurement of cBP involved an invasive procedure that was not feasible or desirable for the general population. Recent technology has increased the availability of several noninvasive techniques to estimate cBP, allowing for the incorporation of this measurement in a multitude of patient populations[16,17,18,19]. This non-invasive technique involves utilizing a BP cuff that operates nearly identically to the traditional peripheral BP measurement devices, yet is also able to calculate central pressure.

The SphygmoCor XCEL system is a non-invasive pulse wave analysis device which uses a brachial pressure cuff placed on the patients arm, over the brachial artery. The brachial systolic and diastolic pressure is captured. The brachial waveform is then analyzed to provide a central aortic pressures and the augmentation index (the extent to which the brachial pressure was augmented by pressure waves). In essence, it is a smarter blood pressure device but uses the same principles as a standard blood pressure device. In addition to the SBP and DBP, it will also provide cSBP, cDBP and AIx.

The evidence that central blood pressure measurements are better predictors of cardiovascular events have led us to evaluate the potential role of this new, innovative technology in diagnosing and treating hypertension[19]. To date this new technology has yet to be incorporated as the standard of care. **However, the preponderance of evidence has led the American Heart Association to release a scientific statement[20] and the American College of Cardiology to call for further studies[21].**

- **Isolated Systolic Hypertension (ISH):** ISH is defined as a diastolic blood pressure (DBP) of ≤ 90 mmHg and a SBP of > 140 mmHg by the World Health Organization[22]. ISH is usually associated with the elderly. However, data from recent studies have shown that ISH is the majority hypertensive subtype in young adult males[23,24,25], with an estimated prevalence ranging anywhere from 6%[25] to over 16%[23,26].

According to JNC 8 guidelines[27,28], ISH patients meet the target blood pressure to initiate pharmacologic treatment for patients younger than 60 years of age. There are four main classes of drugs that are recommended for use as initial monotherapy in uncomplicated hypertension[29]:

- Thiazide Diuretics
- Long-acting calcium channel blockers
- Angiotensin-converting enzyme (ACE) inhibitors
- Angiotensin II receptor blockers (ARBs)

As with any medication therapy, pharmacologic treatment of hypertension can be associated with a multitude of side effects to include palpitations, hyperkalemia, intermittent claudication, upper respiratory infection, increased blood urea nitrogen, hypotension (orthostatic or non-orthostatic), dizziness, syncope and peripheral edema[30]. Several of these side effects pose a significant risk of impacting duty performance for active duty personnel. Respiratory infection would necessitate absence from the duty location. Claudication may negatively impact performance on fitness tests. Hypotension, dizziness and syncope can impair an individual's ability to perform his/her duties, especially if those duties are physical in nature. Additionally, patients with ISH contribute to the direct and indirect costs associated with hypertension each year[31].

Diagnosis of ISH is based solely on measurement of the pressure in the brachial artery. As previously mentioned measurement of pressure at the brachial artery has been the fundamental method for diagnosing hypertension for well over 100 years and is the current standard in routine medical practice. However, measurement of cBP has been shown to be a more accurate predictor of future cardiovascular (CV) events than brachial pressure[9,10,12-14].

As a result of the utilization of non-invasive technology to measure cBP, recent studies have introduced the phenomenon of spurious systolic hypertension (SSH). O'Rourke et al[31] first described SSH in 6 young males. The investigators noted brachial SBP and DBP that were consistent with a diagnosis of ISH. However, utilizing non-invasive cBP measurement techniques, they found that these individuals had a lower than expected central systolic blood pressure (cSBP) and a normal mean arterial pressure. This and other recent studies[24,33,34] have shown that SSH is most common in young men who are physically active and generally taller.

Patients with ISH are most often treated for hypertension. However, recent data suggests that these patients may be receiving unnecessary treatment. Hulsen et al[26] suggested that in patients with SSH, DBP should be the basis for calculating cardiovascular risk to determine whether or not treatment should be initiated. If SSH patients are being treated unnecessarily, this would represent unneeded cost to the patient and/or the health insurance provider in the form of medication and physician office visit costs. It would also indicate that appointment slots, physician office staff time and resources are possibly

being utilized on patients that do not need them. Furthermore, patients may be exposed to medication side effects and are advised of a cardiovascular morbidity that they do not have. In addition, Spruill et al[35] suggested that patients who have received a diagnosis of hypertension are more anxious at future medical provider visits and that this increased anxiety results in a blood pressure reading that is higher than it normally would be (a "white coat effect"). SSH patients who receive a diagnosis of hypertension may continue to present as hypertensive or even experience an increase in blood pressure at medical appointments due to this white coat effect. This may result in increased BP medication doses and more frequent office visits in an attempt to control the perceived hypertension. This results in increased risk of medication side effects for the patient and increased cost of care for both the patient and the health care provider.

At present, 85% of the active duty military population is male with an average age of 28.7 years[36]. Fitness standards require that military members maintain an active lifestyle. These demographics match the demographics of the overwhelming majority of young patients described as having ISH and SSH[26,32,33,34].

Reference Ranges and cBP: While recent advances in medical technology have provided opportunities to measure cBP using non-invasive techniques it has not been widely applied in the outpatient setting and therefore no formal cBP reference ranges have been established. However, these reference ranges are needed in order to validate the non-invasive cBP technology as a diagnostic tool. To date, very few studies[37,38] have attempted to correlate brachial BP and cBP. One such study by Herbert et al[39] only reviewed data from several older non-US populations.

The only available ranges for a "normal" or healthy population are for populations that are significantly older than the active duty military population. One such range, described in Table 3 alongside values for a reference population, included patients with at least one cardiovascular risk factor.[39] the mean ages of the normal and reference populations are 46 and 52 years respectively, both significantly older than the mean age of the active duty military population.

Table 3 Central systolic blood pressure values according to blood pressure categories, for males and females, in the normal and reference populations

	Normal population		Reference population	
	Female	Male	Female	Male
Blood pressure category				
Optimal ($n = 17\,678$) 108 (96, 102, 114, 117)	97 (84, 90, 104, 110) $n = 6415$	100 (88, 94, 106, 111) $n = 4035$	102 (89, 95, 108, 112) $n = 4082$	101 (90, 96, 107, 112) $n = 3146$
Normal (= 9313) 123 (120, 121, 126, 128)	116 (104, 110, 121, 125) $n = 1902$	112 (102, 106, 117, 122) $n = 2669$	116 (107, 111, 120, 123) $n = 2281$	113 (103, 108, 118, 122) $n = 2461$
High normal ($n = 7148$) 133 (128, 130, 136, 138)	126 (115, 120, 131, 135) $n = 1212$	122 (110, 115, 128, 132) $n = 1947$	125 (116, 120, 130, 133) $n = 1861$	123 (111, 116, 128, 132) $n = 2128$
Stage 1 ($n = 3288$) 143 (130, 137, 150, 155)			137 (122, 129, 144, 150) $n = 1276$	133 (119, 126, 142, 148) $n = 2012$
Stage 2 (= 1930) 161 (146, 154, 168, 174)			154 (128, 142, 161, 168) $n = 798$	148 (128, 138, 158, 165) $n = 1132$
Stage 3 ($n = 701$) 183 (162, 178, 193, 206)			173 (153, 164, 183, 194) $n = 312$	171 (143, 158, 183, 192) $n = 389$
ISH ($n = 5255$) 147 (141, 143, 155, 163)			140 (128, 134, 148, 156) $n = 2507$	137 (122, 129, 144, 152) $n = 2748$

Values given here are 50th (10th, 25th, 75th, and 90th) percentiles. Values given below blood pressure categories are for brachial blood pressure.

- Wang et al also suggested diagnostic ranges for cBP in a Taiwanese population with a mean age of 52.3 and 53.6 in the study and control groups respectively[40].

- More research is needed to correlate brachial BP and cBP in a healthy young adult population. We plan to compare the normal reference range seen in the healthy PHA population to that published in the literature so that non-invasive cBP technology may be accurately used to diagnose hypertension. (page 5, Table 3).

- **Physical activity and cBP:** Physical activity has been strongly associated with reduction in BP and cardiovascular disease as a whole[41,42,43]. This is thought to be due to an increase in arterial elasticity associated with physical activity[44]. Current data on the

association between physical activity and BP have been based on measurement of BP at the brachial artery. Although recent advances in technology have made it more feasible to measure cBP, to our knowledge, very few studies have assessed the correlation between physical activity and central hemodynamics. The most comprehensive review of physical activity and central hemodynamics to date was by Laursen et al[45], and reported data for Danish adults aged 40-69 years. To date, there has yet to be a review of physical activity and cBP in an active young adult population in the United States. Because arterial elasticity declines with age[46], an assessment of central hemodynamic data from a population whose arteries should still be elastic could provide valuable predictive data regarding future cardiovascular risk. In theory, those with higher self-reported physical activity should have a lower cSBP and augmentation index (AIx)[34], however this has never been described in a large younger population. Looking at central hemodynamic measurements in an active young adult military population will provide insight into a possible correlation between physical activity and cBP. This will support or strengthen the evidence for military fitness standards.

6.2. Relevance/Significance:

- SSH identification: The results of our analyses will help identify the true prevalence of SSH in a United States active duty military population. Based on data from a study of Danish students[26], it is expected that up to 16% of male active young adults may have SSH and may have been misdiagnosed as having hypertension. This work is critical. The long-term implications may provide sufficient evidence to change the current model of hypertension management and should allow providers to discontinue SSH patient's medication based on CV risk factors.

- Reference range identification: This study will for the first time describe the correlation between standard BP measurements and cBP in an active duty military population. This will aid in the establishment of cBP reference ranges for the diagnosis and management of hypertension based on hypertension class. Improving diagnosis and management of hypertension by establishing cBP reference ranges could enhance identification of long-term patient CV risk, leading to improved morbidity and mortality prognosis.

- Physical Activity Implications: To our knowledge, this study will be the first to attempt to describe the impact of physical activity on cBP in active duty personnel. This could potentially help focus patient centered medical home (PCMH) team intervention strategies for hypertension on the lifestyle factors that have the greatest impact on central aortic pressure.

This analysis will highlight the need to establish clinical practice guidelines for the diagnosis and management of hypertension based on cBP measurements. SSH stands as a prime example of differences (sometimes significant differences) in peripheral BP and cBP measurements. What do we do with these patients? Are they hypertensive? Are they normotensive? Are they

somewhere in between? This analysis will provoke these types of questions within the medical community as a whole and may be a catalyst for action.

The comparison of cBP and brachial BP will provide a starting point with which the medical community will be able to critically analyze cBP data and begin to form a framework for the creation of cBP clinical practice guidelines.

6.3. Hypotheses or Research Questions or Objectives:

Primary Endpoint

1) Prevalence of SSH in an active young adult population at specified intervals over a 3-year period

Secondary Endpoints

1) Compare cBP and brachial BP reference ranges in an active young adult population to that published in the literature.
2) Assess the relationship between physical activity, age, race and gender and cBP in an active young adult population

Exploratory Analysis

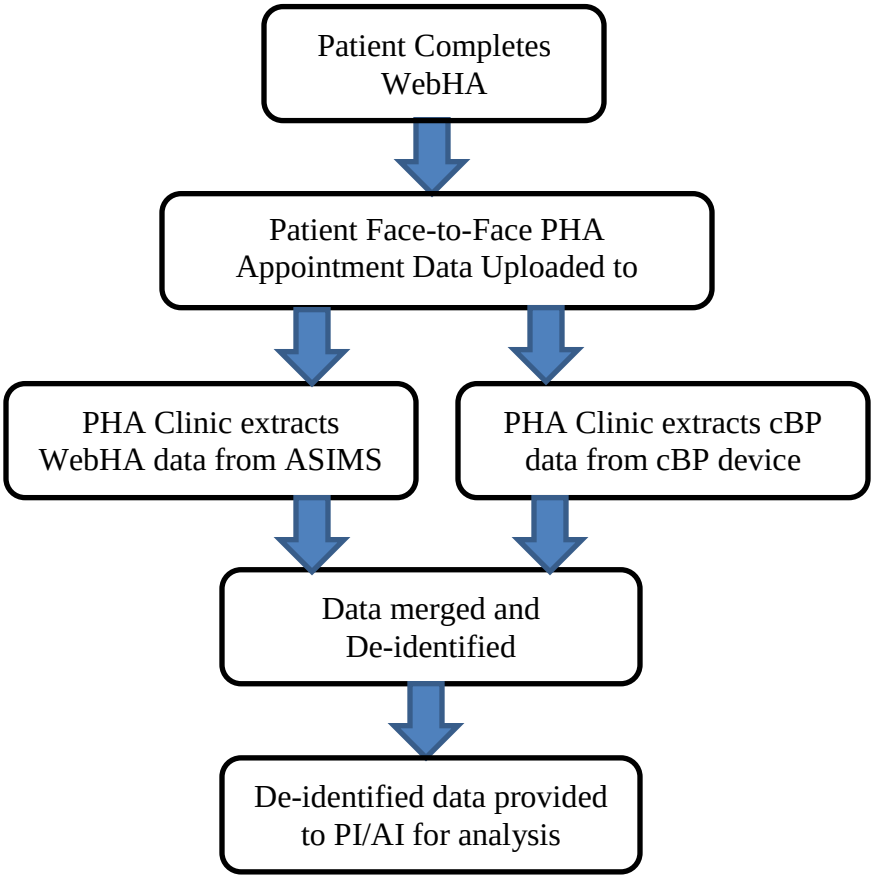
Subgroup Analyses will be completed of the cBP Endpoint using the following data points extracted from the Web Health Assessment (Web HA) patient survey and cBP measurements (explanation of rationale for collecting exploratory data points discussed in section 6.4):

1) Date of Birth (DOB)
2) Standard peripheral Systolic Blood Pressure (SBP)
3) Central Systolic Blood Pressure (cSBP)
4) Standard peripheral Diastolic Blood Pressure (DBP)
5) Central Diastolic Blood Pressure (cDBP)
6) AIx
7) Height
8) Weight
9) Body Mass Index (BMI)
10) Race/ethnicity
11) Patient reported number of vigorous activity days each week
12) Patient reported moderate activity days each week
13) Patient reported muscle activity days each week

6.4. Research Design and Methods:

- RESEARCH DESIGN: Study design is a prospective, descriptive, cross-sectional analysis. The DGMC PHA staff will begin using the SphygmoCor XCEL system (versus Masimo SET Vital Sign Monitor, Welch Allyn, Skaneateles Falls, NY) (Attachment 1 and 2) to measure standard brachial blood pressures on PHA patients that have an in-office appointment. This new technology will also automatically capture cBP data as part of the standard PHA blood pressure measurement.

- RESEARCH METHODS/POPULATION: Data from every patient who had an office blood pressure evaluation during their annual PHA appointment at DGMC over a period of three years will be included in this analysis. The following describes what data will be collected, how the data will be collected, and the purpose of the collected data:



  - The Air Force requires all active duty Air Force personnel to complete an annual PHA at their local base. The purpose of the PHA program is to recommend evidence-based, cost-effective preventive health services and to identify and document potential duty-limiting conditions[47]. The PHA consists of a web-based self-report health status tool, the Web HA, and a face-to-face preventative health visit.

  - The first phase of the PHA is the completion of the Web HA survey. This survey must be completed no earlier than 60 days prior to the PHA face-to-face appointment. The questions from the Web HA survey which are of interest are listed in section 6.3.

- The second phase of the PHA is the face-to-face PHA appointment. During the PHA appointment, the patient's brachial and central blood pressures are taken using a SphygmoCor XCEL system. This system is similar to the currently utilized standard hospital issued automatic blood pressure device. The cuff is placed on the patient's arm over the brachial artery and inflated. During deflation, the cuff's sensory devices enable it to measure and record SBP, DBP, cSBP, cDBP and AIx.

- Under the current PHA clinic process, two blood pressure measurements are to be completed. In the event that both peripheral readings are indicative of hypertension (SBP ≥140 mmHg or DBP≥90mmHg), a third measurement is taken by a member of the PHA clinic staff using a manual brachial blood pressure cuff. If all three measurements are indicative of possible hypertension, PHA clinic personnel create an AHLTA note for the patient and the patient is advised to follow-up with their PCM. Given that there are no current clinical practice guidelines for the diagnosis or management of hypertension using cBP measurements, the PHA clinic will follow their current protocol based on peripheral BP regardless of cBP for the generation of referrals to a PCM. In the event that the third blood pressure measurement with the manual cuff is not indicative for hypertension following two measurements with the SphygmoCor XCEL device that were indicative of hypertension, the SphygmoCor device will be taken offline. PHA clinic staff will contact the device technical support to determine if there is a need for maintenance or repair. If the device is deemed to be functioning correctly, it will be returned to routine use. In the event that the cardiology department recommends a plan of action for management of patients based on cBP measurements, the PHA clinic will follow that plan of action.

- <u>Data to be collected (bolded items are derived from Web HA or cBP device)</u>

  1) <u>BP READINGS</u>:
     - **SBP**
     - **DBP**
     - **cSBP**
     - **cDBP**
     - **AIx**

     This data will be collected for the purpose of analyzing the data set in order to calculate the prevalence of SSH in an active duty military population and to determine correlation between standard BP and cBP in an active duty military population.

- While this project will not impose any changes to the standard procedure for PCM referral when an elevated brachial SBP is evident, we will be using the following cut-off values to determine the prevalence of SSH in the data set[26]:

Brachial SBP ≥ 140 mmHg with central SBP ≥ 124 mmHg	Hypertension
Brachial SBP ≥ 140 mmHg with central SBP < 124 mmHg	SSH
Brachial SBP < 140 mmHg and brachial DBP < 90 mmHg	Normotensive

Measurement of pressure at the brachial artery has been the fundamental method for diagnosing hypertension for well over 100 years and is the current standard in routine medical practice. However, measurement of cBP has been shown in recent studies to be a more accurate predictor of future cardiovascular (CV) events than brachial pressure. The specific markers are cSBP and AIx.

2) SELF REPORTED PHYSICAL ACTIVITY:

- **Number of days in a typical week that "vigorous activity" is performed**
- **Number of days in a typical week that** "**moderate activity" is performed**
- **Number of days in a typical week that** "**muscle activity**" **is performed**

The annual PHA assessment includes three questions on physical activity. Active duty members are asked to estimate the number of days in which they engage in different types of physical activity. The web-based questionnaire defines vigorous physical activity as "activities for at least 20 minutes that caused heavy sweating, or large increases in breathing or heart rate". Some examples of vigorous physical activity are running, lap swimming, aerobics classes or fast bicycling. Moderate activity is defined as "physical activities for at least 30 minutes that caused only light sweating, or a slight to moderate increase in breathing or heart rate". Some examples of moderate activity are brisk walking, bicycling for pleasure, golf, or dancing." Muscle activity is defined as "physical activities specifically designed to strengthen your muscles such as lifting weights, push-ups or sit-ups." Physical activity has been strongly associated with reduction in blood pressure and cardiovascular disease as a whole[41,42,43]. *To date, there has yet to be a review of physical activity and cBP in an active duty military population.* The aggregate cBP data will be analyzed with respect to these responses to measure the degree of correlation of physical activity with cBP. This information could potentially

be used to support the Air Force's current fitness standards. It could also provide evidence for increasing awareness of the impact of physical activity as it is a lifestyle intervention strategy in the prevention of hypertension that is easily actionable for the military and civilian young adult population alike.

3) IDENTIFIERS:
   - **Name**
   - **DOB**

   This data will be used by PHA clinic personnel to match the data collected from the SphygmoCor XCEL system and the web HA data collected from the Defense Health Agency's (DHA) Aerospace Information Management System (ASIMS) office. Additionally, this data will be maintained for the purpose of validating multiple PHA visit appointments over the three year study period. As active duty members complete PHA clinic visits annually, the data from a single patient's second and third visit (or more if the patient elects to schedule a PHA more often than annually) within the study period will not count towards the numerator and denominator for prevalence rate calculations.

4) COVARIATES (known to influence blood pressure, and known associations with SSH):

   [SSH ASSOCIATIONS]
   - **Height**
   - **Weight**
   - **BMI**
   - **Gender**

   Height, Weight, BMI and gender have been suggested in recent studies to be possible predictors of patients with SSH[26,32,33,34]. In these studies, patients with SSH were most commonly male and of increased height, weight and/or BMI. Some of these associations did not reach statistical significance, possibly due to a lack of a sufficiently large patient population. The data set in this analysis will be sufficiently large to provide strong evidence of an association between SSH and height, weight, BMI and gender.

   [RACE/ETHNICITY]
   - **RACE/ETHNICITY**

   Race and ethnicity disparities in the prevalence of high blood pressure have been well documanted[48]. These discrepancies have been based solely on peripheral blood pressure readings. To date, there is no data on the relationship of race/ethnicity to cBP.

- DATA COLLECTION AND EXTRACTION:

The SphygmoCor XCEL system collects the following data; SBP, DBP, cSBP, cDBP and AIx. This data will be extracted from the XCEL system via a data CD in Microsoft Excel format and transferred to a Common Access Card (CAC) enabled computer by a member of PHA clinic staff (Attachment 1: Letter of agreement).

All data that is collected as part of the Web HA survey is reviewed and then processed into ASIMS by a member of the PHA clinic. This data will then be imported from ASIMS into a Microsoft excel format.

The DGMC PHA clinic records all of their clinic data directly into ASIMS. However, the PHA office does not control or maintain this database. Therefore a data sharing agreement (Attachment 3) has been negotiated with DHA's ASIMS office for the PHA clinic to import and review their own clinics biometric and survey data as extracted from ASIMS.

Once this data is extracted, a member of the PHA clinic will match each patient's Web HA data to their corresponding BP data. Because the PHA is an annual requirement for active duty personnel and given current time on station trends, it is anticipated that as much as 70% of second and third year data will consist of repeat patients. For this reason, PHA clinic personnel will maintain identifiable data so as to be able to identify and account for repeat patient data. PHA clinic personnel will de-identify data prior to providing it to investigators. All data will be de-identified at the end of the 3-year study period by PHA clinic personnel. Because PHI and PPI will be stored for up to 3 years, a HIPPA waiver has been requested (Attachment 4).

This protocol seeks approval for prospective data extraction and analysis for a total duration of 3 years. Analyses will be performed accordingly depending on the endpoint of interest.

6.5. Risks/Benefits:

Risks: There is an inherent risk in all medical research of inadvertent disclosure of PHI and PII from a subject's medical record. As such, the investigators of this study will be obtaining de-identified data from the PHA office. SSH is not an established diagnosis so the capturing of cBP parameters will not negatively impact any personnel.

Benefits: There are no direct benefits to patients whose records are included in this review. There is the potential for indirect benefit as the DoD and medical community can

better evaluate and treat hypertension using the modality of noninvasive central blood pressure monitoring.

The unlikely risk of inadvertent leak of clinical data could possibly harm an individual's reputation. However, given that the data being analyzed is already a part of the information being collected by the PHA clinic at DGMC, this risk is well protected against and merits allowing the potential benefit to society of clinical data better describing the impact of the measurement of central hemodynamics in the diagnosis and evaluation of hypertension.

6.6. Subject Population

Age Range: ☒ ≥ 18 y/o ☐ Children (≤ 18)

Sex: ☒ Male ☒ Female

Vulnerable Population: ☒ No ☐ Yes (explain)

Number of Subjects:

- This protocol will use DGMC PHA clinic data from patients seen in clinic over a period of 3 years. It is estimated that the DGMC PHA clinic sees approximately 5,000 patients per year. With one SphygmoCor XCEL unit, the PHA clinic should be able to capture the bulk of the patients seen in the clinic with an upper limit of 5,000 patients/year. While we anticipate an upper limit of 15,000 data points over the 3 year period, the number of individual patients is expected to be approximately 8,000. This is due to approximately an anticipated 60-70% rate of repeat visits over the 3 years. This high rate of repeat patients will allow for analysis of trends over the 3-year period.

Inclusion/Exclusion Criteria:
This protocol will use DGMC PHA clinic data from all patients seen in clinic who received a brachial blood pressure reading during a period of 3 years. Because the PHA is an annual requirement for active duty military members, there is a high likelihood that investigators will receive data sets from the same patient on repeat annual visits. Data sets from repeat visits will NOT be utilized in the calculation of the prevalence of SSH, meaning that only the data from a patient's initial visit to the PHA clinic will be used in this calculation

Data sets from repeat visits WILL be utilized to calculate the correlation between standard BP and cBP measurements in an active duty population. Data sets from repeat visits WILL be utilized to determine correlation between self-reported activity level and cBP in an active duty military population.

Recruitment:

There will be no patient recruitment. Review will be limited to the de-identified records of the DGMC PHA clinic.

Consent:
The study team is requesting a waiver of informed consent as there is no direct intervention or interaction with subjects. As the PHA assessment, patient demographics and patient assessment results are not likely to be damaging to the subject, this proposal seeks IRB expedited review under category 5. Under this expedited review category, informed consent is not required for prospective and retrospective record review (attachment 5).

6.7. Safeguards for Protecting Subjects:
Under this protocol, patient data will be reviewed by investigators of this protocol only. Data will be reviewed via electronic record on CAC enabled computers in private offices.

Data Entry: Data will be extracted by PHA clinic personnel only. Upon completion of data extraction all hard copy documents will be stored as per the hard copy records policy outlined below. All electronic PHI data will be housed on the DGMC EPHI drive and will only be accessible via a CAC enabled computer accessible only to study personnel within a secured office. All electronic transmissions of data will be encrypted over a secured network in a password-protected file.

Data security and transfer: Data transfer will occur via secure EPHI drive and stored on a password- protected Excel spreadsheets. Electronic study related documents, such as this protocol, will reside in the Clinical Investigation Facility or Pharmacy Department as appropriate within the 60MDG SGSE or SGQP Directory in a limited access directory designated exclusively to the study. Access will be granted only to regulatory agencies after a showing of cause, CIF, IRB and study personnel. All de-identified data will reside within a password protected directory designated by study personnel.

To be in compliance with Government regulations study personnel will utilize 128 bit AES encryption. AES is widely used across the government healthcare sector to secure data-at-rest, data-in-motion and data-in-transit. All data transfers will be made via (password protected CD, encrypted Electronic Mail, Secured FTP server, other). All data files will utilize the Advanced Encryption Standard approved cryptographic algorithm used to protect electronic data.

Hard Copy Records: All hardcopy study documents, such as this protocol, will be placed in a locked cabinet and secured area within the IRB Protocol Office at the Clinical Investigation Facility or Pharmacy Department as appropriate. These documents will be accessible only to study personnel, the IRB, and employees of authorized Federal departments and regulatory agencies.

6.8. Data Collection/Analysis:

All PHA data will be extracted and de-identified by PHA staff. The first analysis of the three year data will occur at 3 months with subsequent interim analyses until the three year period of data extraction will be completed. All de-identified data will be provided to the investigators in an excel spreadsheet for review and analysis. All data will be stored on a CAC enabled, password protected file.

Primary Endpoint Analysis Plan:

1) The prevalence rate of SSH in an active young adult population will be computed from the total number of PHA clinic patients with SSH (previously defined) and the total number of PHA clinic patients with BP readings. The prevalence rate will be further stratified by height, BMI, age and gender. As active duty members have PHA clinic visits annually, subsequent visits within the study period will not count towards the numerator and denominator for prevalence rate calculations.

Secondary Endpoints Analysis Plan:

1) Determine the 10^{th}, 25^{th}, 50^{th}, 75^{th} and 90^{th} cSBP percentile for our data set and compare it to published literature [Table 3 in section 6.1]. Compute a correlation coefficient between BP and cBP.
2) The relationship between physical activity, age, race and gender and cBP will be assessed using linear regression. The relationship between the frequency and intensity of exercise, height, BMI, age, gender and cBP parameters will be calculated using a one-way ANOVA.

All other data will be evaluated descriptively to better understand the cohort of our population.

Treatment of missing values: A per-protocol analysis will be performed where all patients with missing data will be dropped for that respective analysis.

Source of Research Material per Participant:

Source of Research Material per Participant	Standard Care	Research Driven
PHA clinic visit	1	0

7. Conflict of Interest

None of the investigators have any conflicts of interest.

8. Investigation Schedule

This protocol intends to review the accumulated DGMC PHA clinic data on a continual basis for a total period of 3 years. Data will be pulled and an interim analysis will be performed quarterly, bi-annually or annually as necessary.

1st year analysis – will meet the Residency Required Research goal for Capt Hedin

2nd and 3rd year analyses – will meet the Residency Required Research goal for Capt McGaughey who needs to show continued research endeavors by faculty for successful residency accreditation.

9. Use of Investigational Drug(s) ☒ No ☐ Yes

10. Use of Investigational Device(s) ☒ No ☐ Yes

11. Support Required
CIF Support:
Support from the CIF will be needed for IRB approval and SG funds management. The CIF bio-statistician consultation may also be sought.

PHA Clinic Support:
Assistance and cooperation of DGMC Public Health PHA Clinic personnel will be needed for data abstraction from DGMC PHA clinic records. (Attachment 6)

12. Budget, Equipment, and Supplies
Requesting Funds: ☒Yes ☐No

☐R&D ☒O&M ☐HMJ ☐OTHER (explain source):

Study Year	Item Description	Unit of Issue (UOI)	Cost/UOI	Quantity	Total Cost
2015-16	SphygmoCor XCEL system	1	$22,270	1	$22,270
2015-16	N-01 Notebook Computer w/ SphygmoCor software	1	$3,060	1	$3,060
2015-16	SphygmoCor XCEL cuff storage tray	1	$327	1	$327
2015-16	SphygmoCor XCEL PWV cuff extra-large adult	1	$84	4	$336
2015-16	Shipping and Handling	1	$150	1	$150
2015-16	Presentation of Results	1	$3000	1	$3000
Total					$29,593

All approved funds will be utilized in the appropriate timeline (July 2016).

☒ I understand that the funding is the responsibility of the PI, which includes; management, tracking, recording and must be reported to the IRB annually with your continuation report

13. Manpower

Rank	AFSC	# hours duty time	# hours off-duty time
Capt Cory Hedin	43P3	200	0
Capt Tracey McGaughey	43P3	120	0
Lt Col Joseph Sky	44M3B	120	0

14. Institutional Official (IO)

Matthew P. Wonnacott, Colonel, USAF, MC
Deputy Commander, 60th Medical Group
David Grant USAF Medical Center
101 Bodin Circle
Travis AFB, CA 94535

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16. Attachments

1) Sphygmocor XCEL 510(k)

2) Sphygmocor XCEL Product Information
3) AF/SG6H Data Request, Agreement and Authorization Form
4) DGMC Application for HIPPA Waiver
5) DGMC Application for Waiver of Informed Consent
6) Letter of support from Public Health Flight Commander

17. Commander's Acknowledgment of Review and Approval

Principal Investigator: I am aware that I am not authorized to accept any funds or other form of compensation for conducting research. All subjects will be treated in compliance with applicable Air Force, DoD and federal regulations, as well as applicable FDA and DHHS guidelines. I have read, understand, and signed the attached Certificate of Compliance. I understand I must complete a review of this protocol at least every 12 months to prevent expiration of the study's approval. I will notify the protocol office **prior** to relocations, separation actions, or closure.

☒ Initial Submission (ALL signatures required)

☐ Amendment Submission (PI signature ONLY)

_____ _____

CORY G. HEDIN, Capt, USAF, BSC Date
Pharmacy Practice Resident

Flight Commander: I have considered this protocol and the personnel and resource support involved. I find this protocol to have sufficient scientific merit for consideration by the Squadron Commander and Institutional Review Board.

_____ _____

JOSEPH G. WEAVER, Col, USAF, BSC Date
Pharmacy Flight Commander

Squadron Commander: I have considered this protocol and I approve the proposed use of Squadron personnel and resource support. I understand that I will be the point of contact for correction of deficiencies should the principal investigator fail to meet the requirements agreed to in the Certificate of Compliance. I find this protocol to have sufficient scientific merit for consideration by the Institutional Review Board.

_____ _____

ANDERSON B. ROWAN, Col, USAF, BSC Date
Commander, 60th Diagnostics & Therapeutics Squadron