Award Number: DAMD17-02-1-0125

TITLE: Hot Flashes among Prostate Cancer Patients Undergoing Androgen Deprivation Therapy: Psychosocial and Quality of Life Issues

PRINCIPAL INVESTIGATOR: James Coyne, Ph.D.
            David J. Vaughn, M.D.
            David Dinges, Ph.D.
            S. Bruce Malkowicz, M.D.
            Nalaka Sudheera Gooneratne, M.D.

CONTRACTING ORGANIZATION: University of Pennsylvania
            Philadelphia, PA 19104

REPORT DATE: December 2006

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
            Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
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# Hot Flashes among Prostate Cancer Patients Undergoing Androgen Deprivation Therapy: Psychosocial and Quality of Life Issues

**Authors:**
- James Coyne, Ph.D.,
- David J. Vaughn, M.D.,
- David Dinges, Ph.D.,
- S. Bruce Malkowicz, M.D.,
- Nalaka Sudheera Gooneratne, M.D.

**Abstract**
Androgen deprivation therapy (ADT) is increasingly prescribed to patients with prostate cancer and brings with it an array of adverse effects. Hot flashes are a common side effect of ADT and are believed to be qualitatively similar to hot flashes among women receiving treatment for breast cancer. Currently no assessment protocols exist for objective assessments of hot flashes in prostate cancer patients, making it difficult to evaluate outcomes in clinical trials, educate clinicians and patients, or develop management and treatment strategies. This project will provide basic clinical epidemiological data concerning the nature, prevalence, and correlates of hot flashes among prostate patients receiving ADT, document the negative effects of hot flashes on sleep, fatigue, and quality of life, and compare the accuracy of alternative means of assessing hot flashes. The overarching goal is to not only understand the nature and importance of hot flashes, but to develop methodological standards for the assessment of hot flashes suitable to diverse applications. Results will have implications for the education of oncologists with respect to quality of life issues in prostate cancer, set standards for future research and clinical endeavors, and suggest directions for patient-oriented research to improve the wellbeing of prostate cancer patients.

**Subject Terms:**
- Prostate cancer
- Hot flashes
- Measurement
- Quality of life

**Security Classification:**
- Report: U
- Abstract: U
- This Page: U

**Number of Pages:**
17
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**Introduction**

Prostate cancer patients are increasingly treated with androgen deprivation therapy (ADT) through chemical or surgical castration, a procedure resulting in the ablation of testosterone, an androgenic hormone which is linked to increased proliferation of prostatic tumors. Hot flashes are a common side-effect of ADT, affecting up to 80% of prostate cancer patients treated with ADT. Although not medically threatening, hot flashes have been associated with sleep disruption, physical discomfort, and significant diminution in quality of life. However, hot flashes are not directly observable phenomena and researchers must usually rely on self-reports of hot flashes, making it difficult to obtain accurate estimates of their frequency and intensity, particularly when hot flashes are nocturnal. Thus, hot flashes and their correlates are not well understood, and the most reliable and valid means of assessment remain unclear.

The current project examines hot flashes among prostate patients receiving ADT through the use of multi-method assessment combining self-report data with objective assessment of sternal conductance and actigraphy. Much of these data will be first of a kind available for prostate cancer patients, particularly data concerning the objective measured occurrence of hot flashes and their relationship to self-report. This investigation will provide descriptive information on the nature, prevalence, and correlates of hot flashes; describe relationships of objectively assessed hot flashes to sleep patterns, fatigue, and quality of life; and compare assessment modalities in their ability to represent the occurrence of hot flashes. Patients participated in a one-week assessment period at baseline and at six-month follow up. Assessment procedures included baseline self-report instruments designed to assess demographic variables, retrospective reports of the frequency and intensity of hot flashes, fatigue, activity level, quality of life, nocturia, psychological distress, and coping. In addition, during each seven-day assessment period, participants completed daily symptom diaries designed to assess the frequency, intensity, and duration of hot flashes, and the life and role interference associated with hot flashes. During this seven-day period, participants were fitted with a small, wristwatch-sized accelerametor designed to record activity-levels during wakefulness and sleep. During two 24-hour periods at the beginning and end of each seven-day assessment period, participants wore a sternal skin conductance monitor designed to objectively assess the occurrence of hot flashes. These sources of data (self-report, actigraphy, and sternal skin conductance) will be combined to allow for a clearer picture of the frequency, intensity, and duration of hot flashes, and, ultimately, will allow for a better assessment of how these influence quality of life and functional status.

**Body**

This project received full human subjects approval by the Department of Defense Grants Officer on March 12, 2003. Since that time, a Postdoctoral Research Fellow served as the position of project manager and meetings with medical personnel and the investigator team were conducted to finalize research procedures. The investigative team convened on a biweekly basis to review the progress of the study and address any challenges to completing the study’s goals.

Research assistants were hired in early 2004 and trained to recruit subjects and collect data during home visits. Janet Carpenter, Ph.D., RN, a grant consultant, who is an expert in the assessment of hot flashes in cancer patients provided three training sessions to study staff on the subjective assessment of hot flashes, the use of sternal conductance monitoring and associated software, and on associated data analyses. Her last site visit was in March 2005. Recruitment of patients began in May 2004, and the first baseline assessment occurred in June 2004. Recruitment and assessment continued until funds were exhausted. The last participant for the ambulatory study was assessed in February 2006. Data entry and quality assurance were completed by June 2006.

A total of 60 men completed the ambulatory assessment making this the largest data set concerning objective assessment of hot flashes in men with prostate cancer that has ever been assembled. Their mean age was 71.4 years (range 54-88 years). The mean body mass index (BMI) was 27.4 +/− 4.3. Most participants were Caucasian (73%). The second largest racial group was African America (25%). The
majority was married or had a partner (78.3%), and had at least a 4 year degree (59.4%). Twenty-five percent of the subjects worked full time and 33.9% of the subjects earned at least $70,000 a year.

In line with our study’s goal of testing the feasibility of sternal skin conductance in men, early assessments revealed some distinct limitations with this mode of hot flash measurement. It should be noted that the view of sternal skin conductance as the “gold standard” for objective assessment of hot flashes has been based entirely on studies of menopausal women and women with breast cancer, and ours is the first study to extend this approach to men. Our study was the first to extend sternal conductance to prostate cancer patients, and of necessity involved recalibrating of the instrumentation, in addition to determining its feasibility and acceptability.

The equipment used in sternal conductance demonstrated some shortcomings when worn by men in their everyday environments, and we worked with the supplier, UFI, to overcome these difficulties. As well, the presence of chest hair proved to be an obstacle to ease of use. Removal of chest hair was not an option, as this also removes skin which, in turn, negatively impacts skin conductance. To overcome this, we conducted literature reviews to find other comparable locations to measure skin conductance that would meet the requirements of sweat gland density and low psycho-activity of sweat glands, and are piloting these alternative sites. In women, a magnitude of $\geq 2$ micromhos, a unite of electrical conductance, in sternal skin conductance has been validated to be the most accurate objective measure of hot flashes. As part of the present project, we have now demonstrated that sternal skin conductance can be used to detect hot flashes in men comparable to its use in women (Hanisch, Palmer, Donahue, & Coyne, in press; Hanisch, Palmer, Donahue, Vaughn, & Coyne, in press). We also collected data for future analysis to determine if skin conductance changes on the upper back can also be used for detecting hot flashes in the event a participant has considerable chest hair.

During the study, we found that measurement artifacts are common. We have identified that placing pressure on the electrode, which participants are likely to do in response to itchiness, as well as exercise and cell phone use creates artifact. As a result, we identified a signature in the sternal skin conductance increase during hot flashes to distinguish artifact from thermoregulation (Hanisch, Palmer, Donahue, & Coyne, 2006). We also created surveys to obtain the reasons why participants refuse to wear the Biolog monitor as well as a survey on the experience of wearing a monitor. Only 22% declined to wear the monitor. The most influential reason for declining was the men thought the monitor would be a burden to wear. Of those who wore the monitor, no major difficulties were encountered and no one removed the monitor during the study. Overall, we took an active, problem-solving approach to tackling problems that are inherent in the assessment of sternal conductance in active, ambulatory persons, but also that are specific to men.

The Hot Flash Questionnaire, which is completed prior to the first 24-hr objective hot flash monitoring session, revealed that 78% of the participants experienced hot flashes. Of those who had hot flashes, the daily hot flash average was 4.7 (SD = 3.9) in the past week and most (53%) reported the duration of their hot flashes to less than 3 minutes. A significant number reported their hot flashes were bothersome a little (46%) and some (35%). The most common symptoms during hot flashes were flushing (61.4%), warmth (100%), and perspiration (95.8%). Hot flashes disrupted sleep more so than activities or relationships. The most common reaction to hot flashes was to do nothing (68%), and 96.7% indicated that they were not receiving hot flash treatment.

Similar to findings among women, there were significant discrepancies between the report of a hot flash and the objective recording of a hot flash (Hanisch, Palmer, & Coyne, 2006). When using the sternal skin conductance criterion for hot flashes developed for women, men experienced 7.4 $\pm$9.2 objective hot flashes and reported a similar frequency of 7.3$\pm$5.3 hot flashes during the recording period. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated to be 44%, 99%, 40%, and 99%, respectively. Thus, men are underreporting the occurrence of hot flashes about 47% of the time and misinterpret somatic or psychosomatic experiences as hot flashes almost 46% of the time. Our contention that subjective reports of hot flashes are inadequate to understand the phenomena has been supported by the current data. This has important implications for future studies of the mechanism hot flashes and calls into question the validity of clinical trials that would rely exclusively on self-report.
These preliminary data suggest that individuals vary greatly in their ability to accurately identify hot flashes, supporting our aim of developing more accurate objective indices of this phenomenon. As a first step, we determined the best indicator of a hot flash for men using sternal skin conductance during a laboratory study (Hanisch, Palmer, Donahue, & Coyne, 2006). Using the criteria established for women of a SCL magnitude of \(\geq 2\) micromho within 30 s, sensitivity to detect subjective hot flashes in the laboratory was 55%, with a PPV of 91%. This compares to a sensitivity of 64% and a PPV of 90% found among menopausal women (de Bakker & Everaerd, 1996). However, analyses of the laboratory data suggest that a better indicator of hot flashes in men consists of a SCL magnitude with a longer duration of 45 s and smaller micromho increase. A magnitude of \(\geq 1.78\) micromho in 45 s increased sensitivity to 68% and provided a PPV of 100%. In ambulatory settings, 31 objective hot flashes in men were detected when using the criteria, \(\geq 1.78\) µmho increase in 45 s. Seventy-one percent of these objective hot flashes were accompanied by an event mark, and 41 event marks occurred in the absence of an objective hot flash. Thus, despite a different criterion for men, inconsistencies between self-report and objective recordings of hot flashes were still present.

Analyses of data from other measures of well-being are in progress. Distress was low as measured by the Hopkins Symptom Checklist (M = 34.7, SD = 6.4) relative to studies of women with breast cancer, but consistent with our earlier studies of androgen deprived prostate cancer patients (Shapiro et al., 2004). Clinically significant distress was found in 7 men. Likewise, health-related quality of life was in the normal range. In general, we found participants had poor sleep as evidence by a mean of \(6.6 \pm 3.2\) in their Pittsburgh Sleep Quality Index (PSQI) global score. Values greater than 5 in the PSQI subscale indicate poor sleep. The Functional Outcomes Sleep Questionnaire (FOSQ) total score revealed that the prostate cancer patients were suffering from mild levels of excessive daytime sleepiness as evidence by a mean of \(18.1 \pm 2.5\). The mean Multivariate Apnea Prediction (MAP) score was \(0.58 \pm 0.19\) and 62% of the subjects had a MAP score greater than 0.5 (the threshold to indicate a high likelihood of sleep apnea). About half felt like their sleep was disturbed by nocturia and 30% felt is caused some or a lot of distress. Relationships between these outcomes as well as for hot flashes are currently being determined.

In the upcoming year, we will continue data analyses for manuscripts and conference presentations. One focus of our analyses will be to provide estimates of the effects of reliance on subjective self-reports as outcome measures in existing clinical trials. We will model the effects on effect sizes. Importantly, we will establish parameters, including a formal power analysis of a study planned for subsequent to this project examining acupuncture in terms of effects on subjective versus objective measures of hot flashes. Aside from allowing evaluation of the mechanism by which acupuncture might affect complaints of hot flashes, this study will provide a model for future research, which based on the results of present study, must now distinguish between objective versus subjective effects of treatment. It is likely that treatments differ in the extent to which they simply affect patient perceptions or self-report versus the occurrence of the objective event of a hot flash.

**Key Research Accomplishments**
- Research staff have been hired and trained.
- Initial referral sources were expanded, active recruitment of patients is completed.
- Databases have been created and data from the full sample have been cleaned and entered.
- Analyses of the data have begun. The first manuscript analyzing data from this study has been accepted for publication.

**Reportable Outcomes**
At this point, no patents and licenses; development of cell lines, tissue or serum repositories; infomatics; funding; employment or research opportunities have been published, applied for, or obtained based on experience with or outcomes of this study.

A review on hot flashes and endogenous opioids has been accepted by *The Lancet* for publication as a comment article. This article credits the DOD for partial support of its preparation. It was published in
January of 2006. A second review drawing attention to parallels between panic and hot flashes has been invited for resubmission to *Psychological Bulletin* (Hanisch, Hantsoo, Freeman, Sullivan, & Coyne, 2006). This paper suggests the rationale for why and how cognitive behavioral interventions might provide a means of alleviating hot flashes that are excessively frequent, intense, or functionally disruptive. *Psychophysiology* has accepted for publication the manuscript analyzing the data from the laboratory study of hot flashes and sternal skin conductance. This paper is crucial for future research, representing the first success in validating a change in sternal skin conductance indicative of a hot flash in men. This paper allows us to move forward in analyzing the relationship between hot flashes and other measures of well-being, as well as further exploring the discrepancies between objectively recorded and subjectively reported hot flashes.

A poster presentation was presented for the annual 2006 Society of Behavioral Medicine conference. The topic was Distress and Hot Flashes in Prostate Cancer Patients Receiving Androgen Deprivation Therapy. A second poster based on the laboratory study has been accepted for presentation at the annual 2007 Society of Behavioral Medicine conference.

**Conclusions**
Since receiving final approval in Year 2, we have finalized procedures, hired and trained staff, and have finished enrolling patients. We have begun analyses of the data and the first paper needed to validate sternal skin conductance as a measure of hot flashes in men has been accepted for publication. Results from this study will have implications for the education of oncologists with respect to quality of life issues in prostate cancer, set standards for future research and clinical endeavors, and suggest directions for patient-oriented research to improve the wellbeing of prostate cancer patients.

**References**

**List of personnel who received salary support during grant period**
Jim Coyne, Laura Hanisch, Anna Rusiewicz, Liisa Hantsoo, Mike Kodransky, Raymond "Chip" Morris, Katharine Barnes, Aletheia Donahue, Mike Russo, John Hergert, Barbara Adams, London Butterfield, Audrey Cleary, David Dinges, Jeff Kraus, Steve Palmer, Davina Rosen, Mohammed Sako, David Segre, Holly Serrao, Martin Szuba, Adrienne Tucker

**Appendices**

Appendix B. Manuscript “Validation of Sternal Skin Conductance for Detection of Hot Flashes in Prostate Cancer Survivors” accepted for publication in *Psychophysiology*, November, 2006.
Both withdrawal and activation of endogenous opioids have been suggested to be mechanisms of menopausal hot flushes. Casper and Yen\(^1\) proposed that hot flushes are hypothalamic thermoregulatory events originating from increased brain norepinephrine activity due to decreased activity of hypothalamic opioids, which in turn is caused by oestrogen withdrawal. Consistent with this hypothesis, it has been proposed that acupuncture reduces the frequency of hot flushes by increasing hypothalamic b-endorphin activity.\(^2\) However, opioid activation has also been suspected because people receiving chlorpropamide flush after drinking alcohol.\(^3\) Research has linked raised norepinephrine and opioids as well as oestrogen withdrawal to hot flushes, but current evidence is insufficient to ascertain the role of opioid withdrawal, due to an absence of studies with appropriate design.

Studies of b-endorphin concentrations in plasma have consistently shown substantial temporary increases after the onset of hot flush. At the point of onset, results are contradictory. Tepper and colleagues\(^4\) found a significant decrease in b-endorphin with use of finger-skin temperature to establish onset of hot flush, whereas Genazzani and colleagues\(^5\) found a significant increase when onset was determined by self report. The different methods of measuring onset, along with varying intervals of plasma collections as long as 20 minutes before the onset of hot flush, might account for the discrepancy.

A substantial limitation of plasma b-endorphin as a measurement of underlying mechanisms is that it may not represent central endorphins that affect thermoregulation. b-endorphin measured in the peripheral blood is more indicative of pituitary release rather than from central secretion.\(^6\) Therefore, the increases in plasma b-endorphin might be an effect of anxiety during hot flushes rather than an initiator of the event. In support of this hypothesis, Genazzani\(^5\) found increases in the stress-related adrenocorticotropic hormone during hot flushes. This hormone is synthesised from the same adenohypophysis precursor molecule, pro-opiomelanocortin, as b-endorphin, and is secreted concomitantly.\(^7\)

Naloxone is an opioid-receptor antagonist used to assess endogenous opioid effects. If hot flushes are caused by opioid withdrawal, the effect of naloxone would be expected to be negligible in postmenopausal women, who have low concentrations of opioids. However, Lightman and colleagues\(^8\) reported that naloxone reduced the frequency of menopausal hot flushes. This result was not replicated in other studies.\(^1,9,10\) The reason for these contradictory findings is unclear.

Despite limitations, the evidence does not suggest that menopausal hot flushes are a result of opioid activation. First, the physiological changes in rats after naloxone parallel the magnitude and temporal order of physiological changes in postmenopausal women during hot flushes.\(^11\) Furthermore, the physical and physiological changes in young adults after naloxone mimic some of the symptoms experienced by postmenopausal women who report hot flushes.\(^12\) Lastly, hot flushes can be diminished with pharmacotherapy that also increases opioid concentrations.\(^13\)

Although a role for opioid activation is questionable, whether opioid withdrawal is involved in the initiation of hot flushes remains unknown. Published work does not address whether opioid withdrawal is linked to oestrogen withdrawal and elevated norepinephrine.\(^1\) No studies have reported on concentrations of opioid peptides in cerebrospinal fluid of postmenopausal women with and without hot flushes. It might be that opioid levels are similarly low in both groups of women, and another biochemical mechanism is responsible for hot flushes. Another possibility is that symptomatic women have a susceptibility to opioid-withdrawal effects due to a genetic polymorphism of opioid receptors.

Naloxone studies might elucidate the role of opioid withdrawal. Blocking opioid receptors in premenopausal women with normal opioid concentrations, or assessment of the re-emergence of hot flushes in postmenopausal women receiving effective treatment for hot flush followed by naloxone,
might be informative. Study design should account for the naloxone dose-response relation to effectively block endogenous opioid systems.\textsuperscript{12}

Determination of the precise mechanisms of hot flushes may be helpful in finding an effective and safe treatment. Another consideration is the distress caused by hot flushes. Anxiety is a predictor of the occurrence as well as the frequency and severity of menopausal hot flushes.\textsuperscript{14} Fluctuations in opioid concentrations during hot flushes might mediate the relation between the severity of symptoms and anxiety. Therefore, low-risk behavioural treatments for anxiety, or alternative treatments that modify opioid concentrations, might be effective. Larger, more detailed studies are needed to identify the mechanisms behind hot flushes and its associated symptoms, and to find safe treatments.

Conflict of Interest

We declare that we have no conflict of interest.

Acknowledgment

We thank Donald F Klein from Columbia University for his contributions to this article. Preparation of this paper was supported in part by the US Department of Defense, Grant #DAMD17-02-1-0125. The content of this publication does not necessarily reflect the views or policies of the Department of Defense.

References


Appendix B

Validation of Sternal Skin Conductance for Detection of Hot Flashes in Prostate Cancer Survivors
Laura J. Hanisch, Steven C. Palmer, Aletheia Donahue, James C. Coyne
University of Pennsylvania

Abstract
The gold standard for objectively measuring hot flashes in women is an increased sternal skin conductance level (SCL), but validation studies in prostate cancer patients are lacking. In the laboratory, an SCL increase of $\geq 1.78$ micro-mho in 45 s had a sensitivity of 68% and a positive predictive value of 100% in detecting self-reported hot flashes among prostate cancer patients. Outside the laboratory, 71% of the objective markers of hot flashes were accompanied by a subjective report of a hot flash, and 65% of subjective reports occurred in the absence of an objective criterion. This study demonstrates that sternal skin conductance can be used to detect hot flashes in men in a manner analogous to its utilization among women. Such use would improve outcome analysis of treatment studies.

Full Manuscript
Hot flashes are prevalent and troublesome in prostate cancer survivors (PCS) undergoing androgen deprivation therapy. A hot flash is a transient sensation of heat or flushing with rapid onset and can be accompanied by sweating, shortness of breath, and dizziness (Quella, Loprinzi, & Dose, 1994). As many as 80% of men undergoing androgen ablation report hot flashes (Karling, Hammar, & Varenhorst, 1994; Schow, Renfer, Rozanski, & Thompson, 1998; Spetz, Hammar, Lindberg, Spangberg, & Varenhorst, 2001), which have been associated with poorer physical well-being (Nishiyama, Kanazawa, Watanabe, Terunuma, & Takahashi, 2004).

The etiology and basic biobehavioral mechanisms of hot flashes remain unresolved and the search for safe and effective treatments continues. Few, if any, placebo-controlled clinical trials of treatments for hot flashes among PCS have been published, but a large placebo effect of up to 66% has been observed in treatment studies of hot flashes among women (Nelson, 2004; Nelson et al., 2006). These effects, however, have been based on self-reported hot flashes, rather than objective measurement. Objective assessment of hot flashes would allow for improved outcome analysis as well as aid studies of the pathophysiology of hot flashes.

The gold standard for objective measurement of hot flashes in women is sternal skin conductance monitoring. Skin conductance is primarily a measure of sweat gland activity and is positively correlated with the number of active sweat glands and their rate of secretion (Dawson, Schell, & Filion, 2000). Skin conductance levels (SCLs) are measured in micro-mho ($\mu$mho), a unit of electrical conductance.

Two laboratory studies with menopausal women showed that 64% and 100% of subjective reports of spontaneous hot flashes were accompanied by a SCL magnitude increase of $\geq 2$ $\mu$mho within 30 s; whereas, 90% and 97% of such SCL increases were accompanied by a subjective report (de Bakker & Everaerd, 1996; Freedman, 1989). During hot flashes triggered through application of heat, 100% of the SCL increases of $\geq 2$ $\mu$mho within 30 s were accompanied by an event mark (Freedman, 1989). These studies also demonstrated that sternal skin conductance was a better measure of hot flashes than other physiological indicators.

Sternal skin conductance as a measurement of hot flashes has not been validated for men, and use of criteria developed for women may not be appropriate as studies of sweat glands in the sternal region have shown sex differences. The density of functioning sweat glands on the chest is suggested to be greater in women than men (Knip, 1969). Moreover, one study found that men had significantly greater sweat secretion rates on the chest during passive heat exposure than women despite similar skin blood flow (Inoue et al., 2005), and another has demonstrated similar results for men and women matched on aerobic capability ($\text{VO}_2\text{max}$) and surface area-to-weight ratio (Frye & Kamon, 1981). Young men had significantly greater sweat rates on the chest than preovulatory, postovulatory, and amenorrheal young women in the first 30-min of exercise as ambient temperature was increasing.
Such sex differences in sweat gland functioning on the chest suggest that the SCL magnitude for detecting hot flashes may be different between men and women. Due to greater sweating rates among males, the base magnitude criterion of 2 µmho for women may be too low for men and result in significant measurement error. This is suggested by one study, which found a significant mean SCL increase of 8.7 µmho during hot flashes among castrated prostate cancer survivors (Spetz, Pettersson, et al., 2001).

However, some research suggests otherwise. The SCL magnitude during hot flashes might be comparable between males and females since sweating declines with age (Armstrong & Kenney, 1993; Inoue, Shibasaki, Hirata, & Araki, 1998) and prostate cancer patients have been older than postmenopausal women within studies of hot flashes (de Bakker & Everaerd, 1996; Hanisch, Palmer, & Coyne, 2006; Spetz, Petterson, et al., 2001). Furthermore, postmenopausal women with hot flashes sweat more on the chest than asymptomatic postmenopausal women and menstruating women (Freedman & Subramanian, 2005). Thus, despite the large SCL increases during hot flashes in prostate cancer patients, it is unclear if the SCL magnitude indicative of hot flashes in menopausal women is valid for PCS (Carpenter, 2005b). Due to a lack of validation studies, we aimed to determine the best SCL indicator of a hot flash in PCS during a laboratory session and to test the laboratory results in real world settings.

Methods

Participants

Eight PCS participating in an ambulatory study of hot flashes and who reported experiencing an average of at least 6 hot flashes a day participated in a controlled laboratory study. Eligibility criteria for the ambulatory study included ongoing androgen deprivation therapy, ECOG criteria of 0-3, and no current radiation, chemotherapy, or myelosuppressive medications. The laboratory participants were recruited from prostate cancer support groups and through fliers. This study was approved by the University of Pennsylvania’s Institutional Review Board, the Clinical Trials Committee of the Abramson Cancer Center, and the General Clinical Research Center (GCRC).

The men gave informed consent, and were paid $100 in compensation. Participants were primarily Caucasian (75%) and most had earned at least a college degree (75%). Their ages ranged from 54 to 83 years and averaged at 68.0 years. All participants were receiving leuprolide, a gonadotropin-releasing hormone agonist. Although one participant ate a diet rich in soy and another drank green tea to control hot flashes, no other medications or therapies intended to reduce hot flashes were used.

Measures

Sternal skin conductance. Skin conductance levels were recorded using a 0.5 constant voltage circuit (Lykken & Venabless, 1971) built in to the front end of single channel of a Biolog® recorder (UFI Model 3992/1 SCL, UFI, Morro Bay, CA) and Meditrace® silver/silver chloride electrodes (Graphic Controls, Buffalo, NY) or Model 1081-HFD silver/silver chloride electrodes (UFI, Morro Bay, CA).1 Electrodes were 1.5 cm in diameter and filled with .05M KCl Unibase/glycol paste (Scheider & Fowles, 1978). The Biolog monitor is a solid state device containing a microprocessor and 2 MB memory. It is powered by a standard 9 volt battery and was programmed to sample 12 bit skin conductance data at 1 Hz (once per second).

Event marking. Participants were instructed to depress the event-mark buttons on the Biolog® when they felt a hot flash occurring. The data was time stamped when the event-mark buttons were pressed. The Biolog® emitted an auditory signal and displayed a visual message on the LCD to alert participants that their subjective hot flash had been recorded.

Hot flash questionnaire. In addition to the event marker, participants recorded the time as well as the severity, bother, duration, and the physical and mental symptoms of the hot flashes. Hot flash severity and bother were measured on a 5-point scale (0=not at all, 4=extreme). The duration of the hot flash was scored as the total number of minutes.

Procedures

Participants were tested individually at the GCRC within the Hospital of the University of Pennsylvania. They did not consume caffeine or alcoholic products 4 hours before testing and did not consume food for 2 hours before and during the entire testing period. During the testing session,
participants were supine on a bed and wore only a light cotton hospital gown. Across testing sessions, the ambient temperature did not drop below 21°C or exceed 26°C.

All participants were connected to the Biolog® monitor by 1030 h. After a 30 min rest for stabilization, monitoring of hot flashes continued until 1500 h. Electrodes were placed two inches below the collar bone and four inches apart centered from the sternal midline. Skin sites were cleaned with alcohol, and any chest hair was trimmed before electrode placement. During the laboratory study, the UFI electrodes became available for testing. Five participants wore the Meditrace electrodes for the first half of the testing session then were fitted with UFI electrodes. The research assistant regularly checked the skin conductance monitor, the participant’s well-being, and ensured that the participant was not sleeping. If a spontaneous hot flash did not occur within three hours, a heating test was administered. Following Sturdee and colleagues (1978), participants were covered with multiple blankets to increase body temperature. If a hot flash did not occur within 30 min, 8 oz of decaffeinated hot tea was ingested to further increase body temperature (Wurster, McCook, & Randall, 1966).

Hot flash data was also collected for 24 hours outside the laboratory. Research assistants met participants at their homes and connected a Biolog® monitor to begin recording at 1100 hour. Participants were instructed to participate in their regular activities with the exception of body-in-water activities (e.g., showering, bathing, or swimming) until the assistant returned the following day and disconnected the monitoring equipment. During the ambulatory monitoring, participants pressed the event marker when they felt a hot flash was occurring.

Data Analysis

First, we examined the concordance between the men’s self-reported hot flashes and the objective criteria of hot flashes previously validated for women. The SCL data and participants’ event marks were recorded on a RAM card in the Biolog® during the monitoring session. Afterward, data were downloaded into a PC via customized software (DPS v.2.1®, UFI, Morro Bay, CA) and graphically displayed on screen. The DPS automatically and sequentially scanned SCL data for an SCL magnitude of $\geq 2 \mu \text{mho}$ within 30 s and flagged such magnitude increases and event marks.

In accord with previous laboratory studies, the occurrence of a hot flash was determined by the participant’s subjective report. A true-positive hot flash was defined as the co-occurrence within a 5-min period of a subjective report and the SCL criterion, and a false-negative hot flash was the occurrence of the subjective report without the SCL criterion. A false-positive hot flash was the SCL criterion lacking subjective corroboration. Sensitivity was calculated as the number of true-positives divided by the sum of true-positives and false-negatives. The positive predictive value (PPV) was determined by the number of true-positives divided by the sum of true-positives and false-positives.

Secondly, the SCL data was analyzed by the Receiver Operation Characteristic (ROC) curve statistic (Green & Swets, 1966) to determine the optimal SCL cut-off point for identification of a hot flash in men. The SCLs for 5 min preceding and 15 min following the self-report of a hot flash were visually scanned for maximum SCL increases in 30, 45, 60, and 75 s. Likewise, maximum increases in 5 randomly-selected 20-min SCL periods during non-hot flash times from each participant were identified so that true-negatives, the absence of both an event mark and specific SCL magnitudes, could be determined. These data were used in the ROC analysis to compute the sensitivity, specificity, and PPV of various SCL magnitudes. Specificity was calculated by the number of true-negatives divided by the sum of true-negatives and false-positives.

To help identify artifact in ambulatory monitoring, descriptive statistics of various parameters of the SCLs were calculated to describe the SCL signature accompanying a subjective report by men in the laboratory. The SCL signature of hot flashes in women is a discrete event characterized by a rapid SCL increase followed by a gradual SCL decline (Carpenter, 2005a). Four minutes of SCLs preceding the peak of the SCL increase during hot flashes were identified and used to calculate two baseline periods. Baseline 1 is the average SCL of the first 30 s of the fourth minute preceding the peak, and baseline 2 is the average of the first 30 s of the third minute preceding the peak. In addition, SCL magnitude changes and the SCL decrease following a hot flash were reviewed.

Lastly, we examined the concordance between objective measurement and subjective report of hot flashes in ambulatory conditions. Trained data analysts reviewed possible hot flash events flagged...
by the DPS to determine a valid hot flash according to the SCL profile (i.e., SCL magnitude and signature) validated for women and identified in this paper for men. Objective hot flashes were compared to subjective reports during waking hours. Waking hours were determined by diary entries of when the men got out of bed for the day and went to bed for the night.

Results

Laboratory monitoring

No technical difficulties were encountered during the laboratory study. Seven men experienced 21 spontaneous hot flashes as indicated by self report. The heating test was administered to one man, who reported one triggered hot flash. Twelve hot flashes were accompanied by the SCL magnitude of ≥2 µmho within 30 s including the heat-induced hot flash. Sensitivity of the SCL magnitude was 55%. The PPV was 92%. In the ROC analysis, the area under the curve for the 30-, 45-, 60-, and 75-s periods was .960, .970, .964, and .966, respectively. Table 1 presents the sensitivity, specificity, and PPV of various SCL magnitude increases in 45 s.

Signatures of laboratory hot flashes. The average SCL for baseline 1 and 2 was 2.93 µmho (SD = 1.39) and 2.99 µmho (SD = 1.47), respectively. All subjective reports of hot flashes were accompanied by a SCL increase. A SCL magnitude of ≥1.78 µmho in 45 s occurred in 68% of subjective hot flashes, and the SCL increase peaked at a range of 1.55 to 22.37 µmho. Except for 1 subjective hot flash, the peak SCL increase occurred after the participants event marked the onset of a hot flash. The time between subjective report and SCL peak ranged from 1 s to 198 s. The SCL at 1, 5, and 10 min after the SCL peak had decreased an average of 2.09 µmho (SD = 2.62), 3.44 µmho (SD = 3.26), 4.46 µmho (SD = 3.91), respectively. See Figure 1 for comparison of sternal conductance increases during hot flashes in the laboratory and ambulatory settings.

Subjective experiences of laboratory hot flashes. All but one subjective hot flash was experienced as a feeling of warmth. Other descriptors of hot flashes included perspiration/sweating (68%), clammy skin (50%), and flushing (32%). No participants indicated that they experienced dizziness, shortness of breath, muscle tension, nausea, dry mouth, headache, heart palpitations, or negative emotions during hot flashes. Hot flashes were not considered very severe (M = 1.59, SD = .80) or bothersome (M = 1.36, SD = .73). Participants reported the duration of hot flashes to be 4 minutes long (SD = 2.02) on average.

Ambulatory monitoring

No technical difficulties were encountered during the ambulatory study. The men averaged being awake for 15.7 (SD = 1.4) hours, and during this time, reported multiple hot flashes (M = 7.88; SD = 3.18; R = 5 - 12). When using the SCL profile developed for women (Freedman, 1989), 24 objective hot flashes were detected. Seventy-five percent of the objective hot flashes were accompanied by an event mark and 45 event marks occurred in the absence of an objective hot flash. Similarly, 31 objective hot flashes were detected when using the criteria, ≥1.78 µmho increase in 45 s, identified in this paper. Seventy-one percent of these objective hot flashes were accompanied by an event mark, and 41 event marks occurred in the absence of an objective hot flash. However, a 45-s magnitude of ≥1.03 µmho returned 82 objective hot flashes, 61% of which were accompanied by an event mark, and only 13 event marks occurred in the absence of an objective hot flash.

Discussion

This is the first laboratory study to determine an objective SCL profile for identification of hot flashes among prostate cancer survivors undergoing androgen deprivation therapy. Using the criteria established for women of a SCL magnitude of ≥2 µmho within 30 s, sensitivity to detect subjective hot flashes in the laboratory was 55%, with a PPV of 91%. This compares to a sensitivity of 64% and a PPV of 90% found among menopausal women (de Bakker & Everaerd, 1996). However, analyses of the laboratory data suggest that a better indicator of hot flashes in men consists of a SCL magnitude with a longer duration of 45 s and smaller µmho increase. A magnitude of ≥1.78 µmho in 45 s increased sensitivity to 68% and provided a PPV of 100%.

The SCL signature of a hot flash was similar between men and women. The SCL increase during a hot flash was a distinct change from the relatively stable SCL preceding the hot flash. Most subjective hot flashes were accompanied by a rapid SCL increase. The SCL decline following the peak was not a
sharp drop but gradual. A comparison of the subjective characterization of hot flashes between men and women is not possible due to lack of or difference in data collection. Among men, hot flashes were primarily experienced as sensations of heat and sweat and were not severe or bothersome. None of the hot flashes lasted longer than 10 minutes; rather, 73% were less than 5 minutes in length.

The SCL magnitude and signature were used conjointly as a profile to distinguish a hot flash event from artifact in the ambulatory study. When the laboratory-based criteria were translated to ambulatory settings, there was some loss of sensitivity to self-reported hot flashes, but the ≥ 1.78 µmho in 45 s criteria continued to perform at higher level than the ≥ 2.0 µmho in 30 s criteria developed among women. The sensitivity of the respective objective markers to detect subjective reports of hot flashes in ambulatory settings was 35% and 29%. The SCL profile for hot flashes established for men also returned fewer false alarms (i.e., subjective report without objective marker) than the women’s SCL profile. This has implications for studies of hot flashes using objective measurement. If a greater SCL magnitude is used to identify hot flashes, results would suggest that the men are not experiencing hot flashes when they report they are, and in addition, treatment might appear more efficacious than it really is, in terms of changes of objectively measured events.

A weakness of this study was the inability to control ambient temperature. Higher temperatures might have impacted SCL increases during hot flashes. This is suggested by increasing sweating rates during heat exposure (Armstrong & Kenney, 1993; Inoue, Shibasaki, Hirata, & Araki, 1998). If this is the case, ambient temperature might need to be a control variable in determining hot flashes in ambulatory studies.

More studies can be conducted to improve the accuracy of skin conductance in detecting hot flashes. It is notable that all subjective hot flashes were accompanied by an SCL increase but that the magnitude ranged from 0.32 to 15.75 µmho in 45 s. Likewise, one laboratory study of young Caucasian males showed individual differences in spontaneous SCL activation and SCL activation following physical exertion (Rickles & Day, 1968). The SCL differences may be a result of dissimilarities in skinfold thickness, VO₂max, sweat gland output, or sweat gland density. In addition, one study of menopausal women suggests that emotional distress might affect the SCL magnitude during self-reported hot flashes (Thurston, Blumenthal, Babyak, & Sherwood, 2005). More studies are needed to determine what factors determine the degree of SCL increases during hot flashes. Additionally, future research using psychophysiological stimuli with participants and matched controls would determine the specificity of the SCL signature during hot flashes.

The SCL profile established in the present study can be used for assessment of hot flashes in ambulatory studies until a more accurate method for detecting hot flashes is developed. The results of objective measures of hot flashes in treatment studies, which have relied to-date on subjective report, could be important towards uncovering the mechanism behind the placebo effect, and in particular, whether this effect is reflected in changes in objectively measured events. Participants may report a decline in hot flashes due to their adaptation to and thus misperception or re-appraisal of the event, rather than the reduced occurrence of hot flashes. On the other hand, it is possible that a placebo response, demonstrated in subjective report but in the absence of changes in objectively recorded events, is nonetheless reflected in improvement in other measures of well-being. If that is the case, then understanding the nature of this placebo response might aid in the development of cognitive-behavioral strategies for the management of the significant discomfort associated with hot flashes.

References


Author’s Note
This research was supported by the US Department of Defense, Grant #DAMD17-02-1-0125 and the Hospital of University of Pennsylvania’s General Clinical Research Center, Grant #RR00040. The content of this publication does not necessarily reflect the views or policies of the Department of Defense or the General Clinical Research Center.

Note
1. Five men provided data using both electrode types. To assess similarity of functioning, hot flash signatures were generated across participants within electrode type. Signatures did not differ in shape or average magnitude of change across 30- (4.8 μmho vs. 4.7 μmho) or 45-s epochs (5.4 μmho vs. 5.4 μmho).

Table 1: Accuracy of sternal skin conductance increases within 45 s for detecting hot flashes reported by prostate cancer patients in the laboratory

<table>
<thead>
<tr>
<th>Magnitude (μmho)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥0.315</td>
<td>100.00</td>
<td>80.00</td>
<td>75.86</td>
</tr>
<tr>
<td>≥0.575</td>
<td>90.90</td>
<td>92.50</td>
<td>86.96</td>
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<tr>
<td>≥1.030</td>
<td>68.20</td>
<td>95.00</td>
<td>88.24</td>
</tr>
<tr>
<td>≥1.780</td>
<td>68.20</td>
<td>100.00</td>
<td>100.00</td>
</tr>
<tr>
<td>≥2.110</td>
<td>59.10</td>
<td>100.00</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Note: PPV = positive predictive value

Figure 1. Mean sternal skin conductance levels during hot flashes reported in the laboratory and in ambulatory settings

Note: Minute zero is the peak of the skin conductance increase