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## Subjective versus objective measurement of hot flushes: Implications for menopause research

In 1981 Ivanna Tataryn and her colleagues discovered that changes in skin conductance are a sensitive and specific indicator of hot flushes [1]. Eight years later Robert Freedman validated the use of skin conductance monitors to measure hot flushes in laboratory and ambulatory research settings [2]. Janet Carpenter then conducted the research needed to demonstrate the feasibility of using a particular monitor, the Biolog (UFI, Morro Bay, CA), in ambulatory research settings [3]. The Biolog continues to be the monitor of choice for many researchers as it reliably detects sweating on the skin by sampling 12-bit skin conductance data at 1 Hz from electrodes placed on the sternum. Although the exact cut-off for detecting physiologic hot flushes may vary across patient populations, a common definition for a physiologic hot flush is a rapid increase in skin conductance of at least 2  $\mu\text{mho}$  [2]. This change in skin conductance is distinct from changes in sweating due to exercise or physical activity. Subjective, self-reported hot flushes can be recorded simultaneously with objective hot flushes in real-time by having the participant press event markers on the monitor.

Increasing numbers of researchers in the field of menopause have used ambulatory skin conductance monitors to measure what are labeled as “physiologic” or “objective” hot flushes. However, there is considerable debate about the use of these monitors due to factors such as variability in concordance rates between subjective and objective hot flushes, under-detection of subjective hot flushes in relation to monitor-detected hot flushes, cross-cultural variation in concordance rates, concerns about acceptability of the method by research participants, and the clinical significance of physiologic hot flushes that are not detected by research participants.

It has long been recognized that there is higher concordance between subjective and objective hot flushes in controlled, laboratory settings than in ambulatory settings [2]. In ambulatory settings, women report about 22–50% of physiologic hot flushes depending on whether they are asleep or awake [4]. Some see this discordance as a methodological limitation and a threat to validity. This discordance is in no way unique to vasomotor symptoms (VMS). Similar inconsistencies have been observed between objective and subjective measurements of cognition, sleep, physical activity and other significant health outcomes [5].

Rebecca Thurston identified several factors that contribute to the discordance between objective and subjective hot flushes. Hot flushes that were reported but did not meet physiological criteria (“false positives”) were preceded in time by increases in negative emotions, decreases in positive emotions, and increases in physical activity, particularly in depressed women [6,7]. Indeed, high negative affect is quite reliably associated with false positives [8]. Further, upon waking women overestimate night sweat frequency compared to monitor-measured flushes [9]. This work shows that discordance between subjective and objective hot flushes should be a topic of further research

rather than a critique of the method, particularly since such work can identify modifiable factors that can improve women’s subjective well-being.

From a clinical perspective a woman’s quality of life is the priority. Hot flushes are a strong determinant of health- and menopause-related quality of life. Frequency and severity are two major dimensions of hot flushes, and of the two, severity has a stronger associations with quality of life. Ambulatory monitors record hot flush frequency objectively, but no dimension of the characteristic change in skin conductance relates to severity or distress [10]. Regulatory bodies, such as the Food and Drug Administration in the United States, recommend that subjective ratings of frequency and severity of vasomotor symptoms be used as two co-primary endpoints in clinical trials. Thus subjective reports are the primary endpoint in clinical trials for hot flush interventions.

Nevertheless, measuring objective hot flushes in clinical trials can be advantageous. A key advantage is that new therapeutics must show greater improvement in hot flushes than placebo. Placebo effects typically range from 31 to 59% for frequency and severity of hot flushes [11]. There is no placebo effect on the monitors [12]. Thus, hot flush monitoring is advantageous in estimating the “true” physiologic effect of an intervention. Monitoring can therefore be helpful in screening new therapeutic interventions and measuring the time course and duration of improvement. In addition to subjective ratings of frequency, monitors also record subjective ratings of hot flush frequency, severity, bother in real time. This attribute greatly minimizes the influence of recall and attention on subjective estimates of hot flush frequency, severity and timing and therefore can improve accuracy, particularly during sleep.

Objective hot flushes are invaluable in characterizing the mechanisms and physiologic correlates of hot flushes. Subjective measures are not optimal due to under-reporting of objective hot flushes, and the influence of psychological factors on subjective reports. Monitors are particularly useful when tracking hot flush events in real time. They have been used to assess the circadian rhythm of hot flushes [13], in neuroimaging studies to identify which brain regions are active before, during and after a physiologic hot flush [14] as well as in cardiovascular studies to demonstrate a decrease in cardiac vagal control during physiologic hot flushes, a decrease that was evident even for hot flushes that women did not subjectively detect [15]. Objective, but not subjective hot flushes, relate to memory performance, brain function, and white matter hyperintensities [16–19], possibly because objective measures are not contaminated by recall, negative affect, and other influences on subjective measures.

Overall, subjective and objective hot flush measures complement each other by offering different benefits in research studies. Only subjective measures estimate severity and bother, which are critical in clinical trials and in other settings where quality of life is of primary

concern. Objective monitoring estimates hot flush frequency in real time, is immune to recall and reporting bias, and shows no placebo response. Those features are key when examining the time course, mechanisms and physiologic correlates of hot flushes.

#### Contributors

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#### Conflict of interest

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