Heart rate variability during high heat stress: a comparison between young and older adults with and without Type 2 diabetes

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Heart rate variability during high heat stress: a comparison between young and older adults with and without Type 2 diabetes. Am J Physiol Regul Integr Comp Physiol 311: R669–R675, 2016. First published August 10, 2016; doi:10.1152/ajpregu.00176.2016.—We examined whether older individuals with and without Type 2 diabetes (T2D) experience differences in heart rate variability (HRV) during a 3-h exposure to high heat stress compared with young adults. Young (Young; n = 22; 23 ± 3 yr) and older individuals with (T2D; n = 11; 59 ± 9 yr) and without (Older; n = 25; 63 ± 5 yr) T2D were exposed to heat stress (44°C, 30% relative humidity) for 3 h. Fifty-five HRV measures were assessed for 15 min at baseline and at minutes 82.5–97.5 (Mid) and minutes 165–180 (End) during heat stress. When compared with Young, a similar number of HRV indices were significantly different (P < 0.05) in Older (Baseline: 35; Mid: 29; End: 32) and T2D (Baseline: 31; Mid: 30; End: 27). In contrast, the number of HRV indices significantly different (P < 0.05) between Older and T2D were far fewer (Baseline: 13; Mid: 1; End: 3). Within-group analyses demonstrated a greater change in the Young group’s HRV during heat stress compared with Older and T2D, the number of significantly different (P < 0.05) HRV indices between baseline and End were 42, 29, and 20, for Young, Older, and T2D, respectively. Analysis of specific HRV domains suggest that the Young group experienced greater sympathetic activity during heat stress compared with Older and T2D. In conclusion, when compared with young, older individuals with and without T2D demonstrate low HRV at baseline and less change in HRV (including an attenuated sympathetic response) during 3 h high heat stress, potentially contributing to impaired thermoregulatory function.

Heart rate variability; hyperthermia; sympathetic nervous system; autonomic response; heat stress

HEAT WAVES lead to negative health outcomes particularly among vulnerable populations such as older adults or individuals with chronic health conditions (e.g., Type 2 diabetes, T2D) (13). A recent investigation assessing the effects of climate change on heat-related illness concluded that future temperature-related mortality will be amplified among the growing aging population (35). Many heat-related deaths occur because of cardiovascular complications. For example, ~94% of deaths reported during the Chicago heat wave in 1995 were attributed to cardiovascular causes (18). Therefore, the initiation of cardiovascular adjustments that help regulate heat dissipation in response to passive heat exposure should be further investigated to advance the understanding of acute age-associated heat-related complications (19).

Heart rate variability (HRV) is a sensitive and noninvasive tool that assesses the time difference between consecutive heartbeats to evaluate autonomic nervous system (ANS) modulation (3). The ANS, an important determinant of cardiovascular function, includes the sympathetic (SNS) and parasympathetic (PNS) nervous systems. HRV indices that reflect PNS activity [e.g., high-frequency (HF) power] have been shown to decline with increasing age (1, 34) and are decreased among individuals with T2D compared with healthy controls (12, 22). An inability of the ANS to reflexively respond to a variety of physiological stressors such as orthostatic stress, meal ingestion, and exercise has been linked to impaired cardiovascular function (8, 25). Furthermore, the initiation of thermoregulatory processes that includes acute cardiovascular adjustments has been linked to fluctuations in ANS activity (8, 23, 25, 29). In response to exercise and during prolonged resting postexercise conditions, age-associated impairments in heat dissipation occurred in adults as young as 40 yr of age (21). Considering the increase in global ambient temperatures and the frequency and severity of extreme heat events, it is reasonable to suggest that age-associated changes in reflexive ANS activity may place older (i.e., ≥60 yr as per present study) individuals at a higher risk of experiencing heat-related impairments in thermoregulatory and cardiovascular function.

It is well established that sensitive fluctuations of HRV occur in response to heat stress (7, 36). In healthy adult males, a short 15- to 30-min period of passive heat stress (35 to 74°C) was sufficient to induce a decrease in HRV (i.e., activation of the SNS and withdrawal of the PNS) (7, 36). Few studies, however, have investigated the influence of prolonged heat exposure on HRV indices measured in an older population (28). Ren et al. (28) reported a decrease in HRV among 694 elderly male volunteers during the summer months in Boston, Massachusetts between 2000 and 2008. The influence of heat exposure on HRV was reported to be stronger as the duration...
of heat stress progressed. The authors suggested that the seasonal change in HRV reflects SNS activation and vagal withdrawal that may increase the risk of cardiovascular-related complications during summer months (28). Thus the gradual rise in mean ambient temperatures accompanied by an expected increase in the elderly population presents a major public health concern. Research investigating the health effects of prolonged heat exposure in vulnerable populations (i.e., older adults or individuals with chronic health conditions) may provide insights for the development of preventative health strategies for acute heat-related physiological complications such as syncope.

To our knowledge, the effects of a prolonged (3 h) exposure to high heat stress (comparable with those typically associated with extreme heat events) on HRV in older individuals with and without T2D remains unknown. The objective of this study was to determine whether older individuals with and without T2D experience differences in HRV during high heat stress compared with healthy young adults. We hypothesized that the older individuals would have lower HRV (i.e., increased SNS and decreased PNS activity) at rest and experience a greater decrease in HRV during heat stress compared with their healthier younger counterparts.

**Study participants.** This case-control study was conducted according to the principles expressed in the Declaration of Helsinki and was approved by the University of Ottawa Health Sciences and Science Research Ethics Board. Exclusion criteria for this study included age (<18 or >75 yr) and history of cardiovascular, respiratory, autonomic (including autonomic and peripheral neuropathies), thyroid, or other chronic diseases apart from T2D. Autonomic and peripheral neuropathies were assessed based on the criteria described by Boulton et al. and Perkins et al., respectively (5, 26). Participants with T2D had been diagnosed for 11.5 ± 4.5 yr, had a hemoglobin A1c level of 7.1 ± 1.0%, no diabetes-related complications, and consistent blood glucose levels throughout the 3-h heat exposure period (Baseline: 7.3 mmol/l; Postexposure: 7.6 mmol/l). The minimum required sample size was determined using data for the difference in cumulative change in body heat storage (92 ± 40 kJ) from a previous study (33) that exposed young and older individuals to a dry-hot environment [36.5°C, 20% RH] during a 30-min heat exposure period (20, 21, 33). The following reviews (6, 30) were required sample size was nine participants per group.

Sixty-six volunteers (41 females) provided written consent and were screened, of whom 8 (~12%) were excluded or lost during follow-up. Thus 22 healthy young adults (Young) and 36 adults [11 adults with T2D and 25 adults without T2D (Older)] matched for body mass and body surface area [i.e., no statistically significant (P > 0.05) differences between groups] participated in this study (Table 1).

**Preliminary measurements.** On a separate day, before the experimental trial, participants visited the laboratory for a preliminary testing session to record age, body height (model 2391, Detecto, Webb City, MO) and weight (model CBU150X, Mettler Toledo, Mississauga, ON, Canada). Also, body density was measured using the hydrostatic weighing technique, and results were used to calculate body fat percentage (accurate to 0.1%) using the Siri equation (32).

**Experimental trial.** Experimental trials were performed in the late fall and winter months between October and March. For each experiment, participants arrived in the morning after eating a light meal and having minimized exposure to thermal stimuli. They were instructed to refrain from intense exercise as well as alcohol and caffeine consumption for 24 h before experimental testing. Upon arrival, participants were prepared and fitted with a 5-lead (EASI) Holter ECG Monitor (DigiTrak XT, Philips Zymed, Andover, MA). Thereafter, participants were asked to remain seated in a rested, comfortable position for 10 min before baseline HRV assessment. Baseline HRV was measured outside of the environmental chamber (20°C, 30% RH) at rest for 15 min while participants were seated. After baseline HRV measurements were completed, participants underwent 3 h of passive heat exposure seated in a semirecumbent position inside an environmental chamber in very hot ambient conditions (44°C, 30% RH). During the heat exposure, participants wore a light pair of athletic shorts and sandals, while females also wore a sports bra. Participants were encouraged to arrive well hydrated as no fluid replacements were provided during the 3-h heat exposure. Urine specific gravity (model TS400, Reichter, Depew, NY) was assessed before participant(s) entered the environmental chamber. Only hydrated volunteers (i.e., urine specific gravity values <1.020) completed the 3-h passive heat exposure session. In addition, HRV data were collected for the entire duration of the heat exposure period.

**Body temperature measurements.** Rectal temperature was measured during the experimental session using a general purpose thermocouple temperature probe (Mon-a-therm General Purpose Temperature Probe, Mallinckrodt Medical, St. Louis, MO) inserted ~12 cm past the anal sphincter. Skin temperature was measured at four locations (i.e., upper back, chest, thigh, and calf) over the left side of the body using 0.3-mm diameter T-type (copper/constantan) thermocouples (Concept Engineering, Old Saybrook, CT) affixed to the skin past the anal sphincter. Skin temperature (Tsk) was subsequently calculated using the following weightings: 30% upper back, 30% chest, 20% thigh, and 20% leg. As previously described (15), body temperature was calculated as the following: 0.86 × (rectal temperature) + 0.14 × (mean skin temperature).

**Heart rate variability measurements.** Data from the Philips DigiTrak XT Holter Monitor worn throughout the experimental session were downloaded and analyzed using Philips Zymed Software (Philips Zymed Version 3.0, Andover, MA). R-R interval data were extracted from the ECG (3 channel at a sampling rate of 175 Hz) tracing, and only beats considered to be normal-to-normal by the Zymed annotation algorithm were retained for further analysis. With the use of the normal-to-normal interval time series of each subject (15-min windowed analysis with 30 s time step), HRV analyses were performed employing the Continuous Individualized Variability Analysis-CIMVA software (http://ohridal.org/cimva/CIMVA-Core-Description.pdf) to extract a total of 55 measures of variability computed from the time, frequency, time-frequency, scale-invariant, entropy, and other nonlinear domains (a list of all 55 HRV variables can be accessed using the following link: https://www.dropbox.com/s/uuuzp4gxlphawh04/ODS.pdf?dl=0). The following reviews (6, 30) of variability analysis techniques and their clinical applications may be viewed for further clarification of the HRV indices calculated for this study.

**Statistical analysis.** Data were tested for normality (Shapiro-Wilk) before analysis. Differences in age, height, weight, body mass index,
percent body fat, and body surface area between groups were tested using a one-way ANOVA. A Bonferroni adjustment was applied to post hoc tests examining pairwise comparisons of subject characteristics. As the majority of HRV data were not normally distributed, nonparametric statistics were used for all HRV analyses. The Kruskal-Wallis rank-based nonparametric test was utilized to determine main effects of group for all 55 HRV indices computed at baseline, as well as at the Mid (82.5–97.5 min) and End (165–180 min) period of the 3-h heat exposure. Mann-Whitney U tests of two independent samples were used to compute between-group post hoc analyses (i.e., Young, Older, T2D) of HRV indices. Main effects of time within each group were analyzed using the Friedman test of k-related samples to determine changes in HRV during heat exposure. Wilcoxon signed-rank tests were utilized to assess post hoc analyses of HRV indices between time points (i.e., Baseline, Mid, End) within each group. Effect size (d) calculations were also utilized for interpretation of pairwise comparisons between groups and across time. As previously described by Cohen (9), levels of effect size data included none (0.0 – 0.19), small (0.2– 0.49), medium (0.5– 0.79), or large (≥0.8). Statistical analyses were conducted using SPSS (Version 23.0) with statistical significance set at \( P < 0.05 \). Results are presented as means ± SD.

RESULTS

Baseline urine specific gravity levels indicated that all groups were adequately hydrated before the start of the passive heat exposure (Young: 1.013 ± 0.007; Older: 1.014 ± 0.008; T2D: 1.018 ± 0.008) (2). All groups experienced similar levels of dehydration following the 3-h heat exposure (Young: 1.023 ± 0.007; Older: 1.023 ± 0.006; T2D: 1.026 ± 0.005) (2).

Young participants had significantly lower percent body fat compared with Older and T2D participants (\( P < 0.05 \); Table 1). Because of space limitations, only 12 (of 55) selected HRV indices that include a variety of statistical/time domain, frequency and complexity measures (commonly described in the literature) (8, 14) are presented in Fig. 1 (coefficient of variation, LF-to-HF ratio, LF power, HF power, Poincaré SD1, and

![Fig. 1. Coefficient of variation (COV), low-to-high frequency ratio computed with Lomb-Scargle periodogram (LF/HF ratio LombScargle), low (LF Power LombScargle) and high (HF Power LombScargle) frequency computed with Lomb-Scargle periodogram, as well as Poincaré plot SD1 (Poincaré SD1) and SD2 (Poincaré SD2) during the 180-min heat exposure in the Young (open bars), Older (solid bars), and Type 2 diabetes (T2D) (shaded bars) groups (means ± SD). msec, milliseconds; s, seconds. *Significant difference from the Young group for the same time point (\( P < 0.05 \)). †Significant difference from the Older group for the same time point (\( P < 0.05 \)).]
Poincaré SD2) and Fig. 2 (Detrended fluctuation analysis: α1 and α2, largest Lyapunov exponent, quadratic sample entropy, multiscale entropy, and Shannon entropy).

Mean heart rate at baseline was significantly lower in the Older group compared with the T2D group ($P < 0.05$; $d = 1.03$; Fig. 3). No other group differences in mean heart rate were detected at baseline or during heat exposure ($P > 0.05$). All groups similarly experienced a significant increase in mean heart rate during heat exposure (main effect of time: $P < 0.05$). Body temperature of the Young group during Baseline, Mid, and End was 36.7 ± 0.3, 37.3 ± 0.3, and 37.5 ± 0.3°C, respectively. Results for body temperature in the Older group during Baseline, Mid, and End was 36.7 ± 0.3, 37.4 ± 0.3, and 37.7 ± 0.3°C, respectively. Finally, body temperature in the T2D group during Baseline, Mid, and End was 36.8 ± 0.3, 37.5 ± 0.3, and 37.7 ± 0.3°C, respectively.

Results from the Kruskal-Wallis test revealed a main effect of group ($P < 0.05$) for 40, 31, and 33 of the 55 tested HRV indices during Baseline, Mid, and End, respectively. Mann-Whitney U post hoc tests showed that compared with the Young group, a similar number of HRV indices were significantly different ($P < 0.05$) in the Older (Baseline: 35; Mid: 29; End: 32) and T2D (Baseline: 31; Mid: 30; End: 27) groups. In contrast, the number of HRV indices significantly different ($P < 0.05$) between the Older and the T2D groups at Baseline, Mid, and End were 13, 1, and 3, respectively. Effect size calculations describing group differences in HRV indices showed similar results and are provided in Table 2.

Results from Friedman’s test revealed a significant difference during heat exposure (main effect of time: $P < 0.05$) in 44, 32, and 23 HRV variables within the Young, Older, and T2D groups, respectively. Results from the Wilcoxon Signed-Rank post hoc tests and effect size calculations (Table 3) suggest that the Young group’s HRV was more responsive to the 3-h heat stress compared with both the Older and T2D groups. The number of significantly different ($P < 0.05$) HRV
indices between Baseline and Mid was 34, 25, and 19 for the Young, Older, and T2D groups, respectively. Similarly, the number of significantly different (P < 0.05) HRV indices between Baseline and End was 42, 29, and 20, for the Young, Older, and T2D groups, respectively. Finally, the number of significantly different (P < 0.05) HRV indices between Mid and End was 24, 8, and 6, for the Young, Older, and T2D groups, respectively.

**DISCUSSION**

The aim of the current study was to determine whether older individuals with and without T2D experience differences in HRV during a prolonged 3-h exposure to a very high heat stress environment (comparable with conditions experienced during an extreme heat event) compared with young healthy adults. The findings suggest, that within the studied population, young individuals’ HRV was more responsive to the 3-h heat stress compared with older individuals with and without T2D. In general, these findings do not support our hypothesis. Although the older individuals had lower HRV (i.e., increased SNS and decreased PNS activity) at rest, these participants did not experience a greater decrease in HRV during heat stress compared with young healthy adults.

Young participants assessed in the current study clearly demonstrated vagal dominance compared with the older adults at baseline. Specifically, HRV indices characterizing PNS activation (e.g., HF power, Poincaré SD1 and SD2, Shannon Entropy, and Quadratic Sample Entropy) were elevated in the young adults compared with the older individuals with and without T2D. These data are consistent with a number of published reports that show an age-associated decline in HRV (i.e., vagal input) (1, 4, 34, 37). For example, Bommemeier et al. (4) analyzed 24-h time-domain HRV indices in 166 healthy adults between the ages of 20–70 yr and concluded that an adult age between the ages of 20–70 yr and concluded that an age-associated decline in cardiac vagal modulation is a normal response to the aging process. There are, however, a few studies that have reported a progressive increase (or recovery) in PNS activity during the seventh or eighth decade of life that follows the aforementioned age-associated decline (1, 37). This was not evident in the current study given that the majority of the older participants were just entering their seventh decade.

A large number of HRV indices were different between groups at baseline and during heat stress. The number of significant HRV variables and the corresponding effect size calculations support that the younger individuals in the current study experienced greater ANS activation during heat stress compared with the older individuals with and without T2D. At baseline, young individuals had 35/55 and 31/55 HRV indices that were significantly different from the Older and T2D groups, respectively. Similarly, at the end of the heat stress period, Young individuals had 32/55 and 27/55 HRV indices that were significantly different from the Older and T2D groups, respectively. Furthermore, the younger individuals had greater SNS activation during heat exposure compared with the older individuals with and without T2D. For example, at baseline the low-frequency (LF) power and HF power ratio (LF/HF) ratio was similar between groups. During heat stress, however, LF/HF was significantly higher in the Young group compared with both the Older the T2D groups. In addition, HF power was elevated in the Young group at baseline (compared with the Older and T2D groups) but was similar to the Older and T2D groups during the heat exposure period. Other HRV indices that are primarily influenced by vagal activity were either elevated (e.g., coefficient of variation) in the Young group or similar (e.g., Poincaré SD1) in all groups during heat stress. Additional HRV data (e.g., LF power and DFA Alpha 1) shown in Tables 2 and 3 demonstrate similar results. Overall, our HRV results show that the Young group experienced greater SNS activation and similar or slightly elevated vagal activity during heat stress compared with the Older and T2D groups. These data support previous findings that showed ANS activity in young adults is characterized by SNS dominance during heat stress (10, 11, 14, 24). Older individuals, however, in the current study displayed a weak SNS response to passive high heat stress exposure. These findings are in contrast to Gagnon et al. (17) who reported no difference in muscle SNS activity between young (28 ± 4 years) and aged (70 ± 5 years) participants during ~65 min of passive heating. There were, however, differences in heat exposure time and implementation as well as in the method of assessing SNS activity between Gagnon et al. and the current study.

Regulation of body temperature during an acute exposure to environmental extremes has been proposed to be influenced by the SNS (23, 29). Sawasaki et al. (29) investigated the SNS regulation of body temperature during an acute exposure to environmental extremes and found that T2D individuals with Type 2 diabetes had lower SNS and greater PNS activity during heat stress compared with the Older group or similar (e.g., Poincaré SD1) in all groups during heat stress.

**Figure 3.** Heart rate during the 180-min heat exposure in the Young (open bars), Older (solid bars), and T2D (shaded bars) groups (means ± SD). †Significant difference from the Older group for the same time point (P < 0.05).
response to local cooling and found that the volunteers with a marked SNS response to cold stress were able to maintain their core temperature. Another study reported an increase in SNS activation (determined by LF/HF) during an acute cold and heat stress that was related to perceived thermal comfort levels. The authors proposed that fluctuations of LF/HF may be an important physiological indicator of thermal comfort and thermoregulatory function (23). Thus an efficient SNS response during acute exposures to environmental extremes may be important for the initiation of the heat loss responses of sweating and skin vasodilation; responses critical to the regulation of body temperature during heat stress. Data from the present study suggest that the young individuals experienced greater SNS activation in response to high heat stress exposure compared with the older individuals with and without T2D. Specifically, the younger individuals had 42/55 HRV indices that were significantly different between baseline and the end of the heat stress period. Only 20/55 and 29/55 of HRV indices were significantly different between baseline and the end of the heat stress period for the older individuals with and without T2D, respectively. When the HRV indices that were influenced by heat stress within each group were examined, it is further supported that the Young group experienced a greater SNS response to heat stress. For example, LF/HF ratio significantly increased from baseline to the end of the heat stress period only within the Young group. As described above, these data suggest that the Young group’s SNS was more responsive during heat stress and therefore may be more physiologically prepared for initiating thermoregulatory processes. Furthermore, with the consideration of the potential link between LF/HF and thermoregulation, a weak SNS response (determined by LF/HF) to heat stress may delay thermoregulatory processes to defend against increases in body heat storage and place the older individuals at greater risk of experiencing an acute heat-related complication such as syncope (23).

In the current study, SNS activity in the older individuals with and without T2D was less responsive during heat stress compared with the younger volunteers. These data indicate that older individuals may be less able to initiate thermoregulatory processes during an acute exposure to environmental extremes and may explain, at least in part, increased heat-related complications among older populations. It is, however, important to mention that there were no differences found in mean body temperature between groups. There are a few studies that have recently challenged the appropriateness of using thermometry (e.g., core temperature) as a way to assess whole body thermal strain. Stapleton et al. (33) found that older individuals store more heat and experience increased thermal strain compared with young individuals when exposed to a hot environment (36.5°C, 20% RH for 2 h; temperature in Canada rarely exceeds this level) that resulted in a much lower level of heat stress compared with the current study (44°C, 30% RH for 3 h); conditions representative of those recorded in the extreme heat events of 2003 in Europe, 2010 in Russia, and 2015 in India (16, 27, 31). Stapleton et al. (33) also reported an increase in visceral and mean skin temperatures during heat exposure but found no difference between the young and older groups. Thus the interpretation of core temperature compared with body heat storage may lead to different conclusions regarding the risk of experiencing a heat-related emergency. Future research should consider the direct relationship between HRV and thermoregulatory processes, including body heat storage, during heat stress. This would provide further support for altered ANS activation as a potential mechanism for impaired thermoregulatory processes among an older population. The relationship between HRV and thermoregulation may provide insights for the development of preventative public health strategies to counter the impact of increasing ambient temperatures on the growing aging population.

In conclusion, older individuals with and without T2D in the current study experienced an attenuated SNS response to 3 h of high heat exposure compared with young healthy adults. These findings suggest that SNS activation during an acute high heat stress could serve as a protective thermoregulatory response that may be impaired among older individuals with and without T2D. A weak SNS response to high heat stress may put older individuals at a greater risk of experiencing an acute heat-related complication.

**Perspectives and Significance**

Elevated SNS activity is common during heat stress and may be involved in the initiation of thermoregulatory processes such as sweating and skin vasodilation (23, 29). Thus a weakened SNS response to heat stress, as experienced by the older individuals in the current study, may impair their ability to thermoregulate. The contention is that an increased risk of experiencing an acute heat-related complication could occur during a heat wave if the individual experiences a weakened SNS response that impairs the ability to initiate thermoregulatory processes. If a weak SNS response during a heat wave does result in an impaired initiation of thermoregulatory processes, strategies could be developed and implemented in vulnerable populations that lead to efficient SNS activation in response to heat stress. This provides an interesting avenue for future research that could have important public health implications considering the global rise in ambient temperatures and the increasing aging population.

**GRANTS**

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**Table 3. Number of variables for different levels of effects size (out of 55 HRV variables calculated) for comparisons within groups at baseline and during heat exposure**

<table>
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<tr>
<th>Comparison</th>
<th>Level of d</th>
<th>Young</th>
<th>Older</th>
<th>T2D</th>
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<td>Baseline vs. Mid</td>
<td>None</td>
<td>8</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>Small</td>
<td>15</td>
<td>11</td>
<td>13</td>
<td></td>
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<tr>
<td>Medium</td>
<td>14</td>
<td>14</td>
<td>11</td>
<td></td>
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<tr>
<td>Large</td>
<td>18</td>
<td>10</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Baseline vs. End</td>
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<td>8</td>
<td>14</td>
</tr>
<tr>
<td>Small</td>
<td>11</td>
<td>16</td>
<td>16</td>
<td></td>
</tr>
<tr>
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<td></td>
</tr>
<tr>
<td>Large</td>
<td>31</td>
<td>16</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Mid vs. End</td>
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<td>35</td>
<td>28</td>
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<tr>
<td>Small</td>
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</tr>
<tr>
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<tr>
<td>Large</td>
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T2D, Type 2 diabetes, Mid (82.5–97.5 min during heat exposure); End (165–180 min during heat exposure). Levels of d include none (0.0–0.19), small (0.2–0.49), medium (0.5–0.79), and large (≥ 0.8).
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DISCLOSURES
C. L. Henry is a patent holder related to waveform quality assessment for variability analysis and variability derived clinical decision support. A. J. E. Seely is Founder and Board Chair of Therapeutic Monitoring Systems (TMS); TMS is developing and commercializing waveform-based variability-derived clinical decision support tools to improve care for patients at risk for or with existing critical illness. Otherwise, there are no conflicts of interest to declare, financial or otherwise.

AUTHOR CONTRIBUTIONS

REFERENCES