Sex differences in the modulation of vasomotor sympathetic outflow during static handgrip exercise in healthy young humans

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PREMENOPAUSAL WOMEN TYPICALLY have lower resting blood pressure (BP) (9, 14, 17) and lower incidence of cardiovascular disease (24) than similarly aged men, but the underlying mechanisms are not completely understood. The hormone profile of premenopausal women suggests that estrogen and/or progesterone provide a degree of cardioprotection (27, 39). BP reactivity has been described as one predictor of the future development of hypertension (1, 8). Based on this, we would hypothesize that premenopausal women would have an attenuated vasomotor sympathetic response to static exercise, which would be further reduced during the high sex hormone [midluteal (ML)] vs. the low hormone phase [early follicular (EF)]. We measured heart rate (HR), blood pressure (BP), and muscle sympathetic nerve activity (MSNA) in 11 women and 10 men during a cold pressor test (CPT) and static handgrip to fatigue with 2 min of postexercise circulatory arrest (PECA). HR increased during handgrip, reached its peak at fatigue, and was comparable between sexes. BP increased during handgrip and PECA where men had larger increases from baseline. Mean ± SD MSNA burst frequency (BF) during handgrip and PECA was lower in women (EF, P < 0.05), as was ΔMSNA-BF smaller (main effect, both P < 0.01). ΔTotal activity was higher in men at fatigue (EF: 632 ± 418 vs. ML: 598 ± 342 vs. men: 1,025 ± 416 a.u./min, P < 0.001 for EF and ML vs. men) and during PECA (EF: 354 ± 321 vs. ML: 341 ± 199 vs. men: 599 ± 327 a.u./min, P < 0.05 for EF and ML vs. men). During CPT, HR and MSNA responses were similar between sexes and hormone phases, confirming that central integration and the sympathetic efferent pathway was comparable between the sexes and across hormone phases. Women demonstrated a blunted metaboreflex, unaffected by sex hormones, which may be due to differences in muscle mass or fiber type and, therefore, metabolic stimulation of group IV afferents.

Cold pressor test; muscle sympathetic nerve activity; metaboreflex

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MATERIALS AND METHODS

Subjects

Twenty-one (11 women, 10 men) healthy volunteers were studied. Descriptive characteristics of the subjects are outlined in Table 1. Exclusionary criteria included: significant medical history, smoking, recreational drug use, hormonal contraceptive use within the previous 6 months, and current pregnancy. Additionally, subjects that were endurance trained were excluded from participation. All female participants were normally menstruating (i.e., ~28-day cycle). All subjects gave written informed consent to participate in the study, which was approved by the Institutional Review Boards at the University of Texas Southwestern Medical Center and Texas Health Presbyterian Hospital Dallas.

Measurements

HR and BP. HR was determined from lead II of the electrocardiogram (ECG). BP was assessed using two methods. Beat-by-beat arterial pressure [systolic BP (SBP); diastolic BP (DBP)] was estimated noninvasively by using finger photoplethysmography (model 1, Nexfin HD monitor; BMEYE, Amsterdam, The Netherlands). This method was used to examine BP changes during static handgrip to fatigue and the cold pressor test (CPT). BP was also obtained via electrophygomonanometry (model 4240; SunTech Medical Instruments, Raleigh, NC) with a microphone placed over the brachial artery to detect Korotkoff sounds. This method was used to obtain baseline BP values when the subject was initially instrumented in our laboratory to ensure a resting steady state had been achieved before fatigue and the cold pressor test (CPT). BP was also obtained via the wrist in an ice water bath (4°C) for 2 min, which was followed by 3 min of recovery. Subjects were instructed to avoid breath holding (confirmed by nasal cannula) and to stay as relaxed as possible.

Static handgrip to fatigue. After at least a 5-min recovery phase from the CPT, static handgrip was performed at 40% of MVC until fatigue. This level of force was chosen since it has been previously shown that handgrip sustained at 40% and 60% of MVC elicited comparable increases in BP and MSNA at fatigue (30). Since individuals can sustain 40% of MVC for a longer period of time, this allowed for a better assessment of the time course, as well as for comparisons between studies (i.e., studies that stopped handgrip at 2 min). Once the exerted force declined to <80% of the desired force for ≥2 s, a 2-min PECA (with an upper arm cuff inflated to 250 mmHg) phase began. During static handgrip exercise and PECA, subjects were instructed to avoid breath holding (confirmed by nasal cannula).

Data Analysis

Data were sampled at 625 Hz with a commercial data acquisition system (Biopac Systems, Santa Barbara, CA) and analyzed using LabView Software (National Instruments, Austin, TX). Beat-by-beat HR was calculated from the R-R interval of the ECG. Beat-by-beat SBP and DBP were estimated from the arterial waveforms. MSNA bursts were identified by a computer program using a 3:1 signal-to-noise ratio threshold within a 0.5-s search window and an expected burst reflex latency of 1.3 s from the preceding R-wave (5). All bursts were confirmed by trained personnel. Burst areas of the integrated neurogram and BP were measured simultaneously on a beat-to-beat basis. Burst frequency (BF) was defined as the number of bursts per min, and burst incidence (BI) was used to normalize BF per 100 heart beats. Total activity was defined as the burst area of the rectified and integrated neurogram. We used a modified method developed by Sugiyama et al. (34) and Halliwill (13) where we defined the burst area of the rectified and integrated neurogram. We used a modified method developed by Sugiyama et al. (34) and Halliwill (13) where we assigned the largest burst amplitude during baseline a value of 100. Therefore, all other bursts within a testing session were normalized against this value. For comparisons between groups (men vs. women) and across sessions (EF vs. ML) we report the change in total activity from baseline (Atotal activity).

Baseline MSNA, HR, and BP for both the static handgrip exercise and CPT were averaged for 1 min. The total handgrip time was divided evenly into five stages, and the data were presented as 20, 40, 60, 80, and 100% (at fatigue) (30). Stages during handgrip were divided accordingly because subjects performed handgrip until fatigue by an ovulation prediction kit (OvuQuick; Quidel, San Diego, CA). Hormone concentrations were verified on each study day. For the 2 days prior to testing, all subjects were on an isocaloric constant diet consisting of 200 meq sodium, 100 meq potassium, and 1,000 mg calcium, while water intake was ad libitum. Female subjects submitted a urine sample for pregnancy testing prior to any of the experimental procedures.

The experiment was performed ≥2 h after a light meal and ≥48 h after the last caffeinated or alcoholic beverage was consumed. The laboratory was environmentally controlled with an ambient temperature of ~25°C. Each subject was studied in the supine position. Prior to microneurography, subjects performed three brief (~3 s) maximal contractions with his/her dominant hand to determine his/her maximal voluntary contraction (MVC) by using a handgrip dynamometer. Baseline data collection began at least 10 min after an acceptable nerve recording was obtained.

CPT: We used the CPT as a secondary probe of sympathetic neural control between the sexes, as others have used it to assess the central integration of vasomotor processes and their efferent pathways (26, 31, 37). CPT-induced increases in BP and HR involve the activation of the rostral ventrolateral medulla and the nucleus ambiguous (26, 27), two brain structures responsible for pressor and tachycardic responses.

Following 1 min of baseline, the dominant hand was immersed up to the wrist in an ice water bath (4°C) for 2 min, which was followed by 3 min of recovery. Subjects were instructed to avoid breath holding (confirmed by nasal cannula) and to stay as relaxed as possible.

Table 1. Subject characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Women</th>
<th></th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>33 ± 10</td>
<td>33 ± 10</td>
<td>32 ± 10</td>
</tr>
<tr>
<td>Height, cm</td>
<td>165.9 ± 5.9*</td>
<td>165.5 ± 6.1*</td>
<td>176.0 ± 6.0</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>63.7 ± 7.5*</td>
<td>63.8 ± 7.7*</td>
<td>79.1 ± 12.0</td>
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<tr>
<td>Body surface area, m²</td>
<td>1.7 ± 0.1*</td>
<td>1.7 ± 0.1*</td>
<td>2.0 ± 0.2</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.1 ± 2.1</td>
<td>23.3 ± 2.1</td>
<td>25.3 ± 3.1</td>
</tr>
</tbody>
</table>

Values are means ± SD; n = 11 women, 10 men. EF, early follicular phase; ML, midluteal phase. *Different from men, P < 0.01.
and this served as a way to normalize for intersubject variability. PECA 1, PECA 2, and recovery (REC 1, REC 2, REC 3) data were averaged each minute. Stages for the CPT were averaged every 30 s.

Statistical Analysis

Data are expressed as mean ± SD. A two-way repeated-measures ANOVA [group (men, EF, ML) × stage] was used to examine cardiovascular and MSNA responses to the static handgrip exercise and CPT between the sexes and menstrual phases. A separate two-way repeated-measures ANOVA [group (men, EF, ML) × stage] was used to assess differences between the sexes in terms of their response to these perturbations by examining the change (Δ) from baseline for each variable. Tukey’s post hoc analysis was used when significance was found. All statistical analyses were performed using SigmaStat 3.11 (Systat Software, San Jose, CA). A P value of <0.05 was considered statistically significant.

RESULTS

Hormone Analyses

Estrogen was lower during the EF phase compared with the ML phase (32.4 ± 8.9 vs. 91.8 ± 46.7 pmol/l; P < 0.01). Progesterone was also lower during the EF phase (0.9 ± 0.5 vs. 11.1 ± 5.7 nmol/l; P < 0.01). Low vs. high sex hormone status did not influence the absolute BP or the magnitude of the change in BP in women. However, there was no difference in HR response from baseline to fatigue between the two phases of the menstrual cycle (P = 0.47). Finally, HR returned to baseline values during PECA in both women and men, with no difference between phases of the menstrual cycle.

BP

The BP responses to static handgrip and circulatory arrest are shown in Table 2 and Fig. 2. SBP and DBP in all groups was higher at fatigue (all P < 0.001) and during PECA (all P < 0.001) compared with baseline. The men had higher SBP and DBP compared with women at fatigue and PECA (all P < 0.01), as well as demonstrated a greater ΔSBP and ΔDBP from baseline to fatigue and during PECA (all P < 0.01). Low vs. high sex hormone status did not influence the absolute BP or the magnitude of the change in BP in women.

MSNA

MSNA (Table 2 and Fig. 3) progressively increased during static handgrip in both sexes, reached the peak at fatigue, and remained elevated during PECA compared with baseline (all

Vascular Transduction

During static handgrip (at fatigue and during PECA 2) the change in MSNA and DBP from baseline was lower in the women. However, there was no difference in the vascular transduction (ΔDBP/Δtotal activity) between the sexes in either condition (EF: 0.03 ± 0.02 units vs. ML: 0.04 ± 0.05 vs. men: 0.03 ± 0.01 at fatigue, P = 0.66; EF: 0.04 ± 0.04 vs. ML: 0.05 ± 0.07 vs. men: 0.04 ± 0.02 units during PECA2, P = 0.69).

CPT

HR. Figure 4 shows the cardiovascular responses to the CPT. HR increased immediately and was significantly
DISCUSSION

The present study is the first to comprehensively examine responses to static handgrip exercise and a cold pressor stimulus in a group of men and women, while controlling for low vs. high hormone phases in the women. The principal findings

higher compared with baseline during the CPT ($P < 0.001$). The change from baseline ($\Delta$HR, Table 2) was similar between men and women, as well as between phases of the menstrual cycle.

BP. SBP and DBP (Table 2 and Fig. 4) also increased during the CPT in both groups ($P < 0.05$). The magnitude of the change compared with baseline ($\Delta$SBP and $\Delta$DBP, Table 2) was significantly higher in the men during the peak response (at 1.5 min) compared with the women during both phases of the menstrual cycle ($all < 0.05$). The absolute DBP was higher in men compared with women in the EF during the CPT ($all < 0.05$). Although it appears that absolute SBP and DBP was higher during the high hormone phase compared with the low hormone phase of the menstrual cycle in the women, there was no statistical difference. The women demonstrated similar increases ($\Delta$) in SBP and DBP during the both low and high hormone phases of the menstrual cycle.

MSNA. MSNA is illustrated in Fig. 5. MSNA-BF was significantly higher during the CPT compared with baseline ($P < 0.001$). MSNA-BI showed a similar trend ($P < 0.001$). $\Delta$MSNA-BF was similar between the sexes; however, the men had a significantly greater $\Delta$MSNA-BI compared with women in the ML phase because women had higher HRs (Table 2, $P < 0.05$). $\Delta$Total activity was not different between the sexes. Low vs. high sex hormone status did not affect any of the MSNA variables in the women.

Table 2. Cardiovascular and vasomotor sympathetic outflow changes during static handgrip exercise and cold pressor test (CPT)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Static Handgrip</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100%, at fatigue</td>
</tr>
<tr>
<td>$\Delta$HR, beats/min</td>
<td></td>
</tr>
<tr>
<td>Women, EF</td>
<td>15 ± 7*</td>
</tr>
<tr>
<td>Women, ML</td>
<td>12 ± 9*</td>
</tr>
<tr>
<td>Men</td>
<td>24 ± 6</td>
</tr>
<tr>
<td>$\Delta$SBP, mmHg</td>
<td></td>
</tr>
<tr>
<td>Women, EF</td>
<td>22 ± 13*</td>
</tr>
<tr>
<td>Women, ML</td>
<td>16 ± 12*</td>
</tr>
<tr>
<td>Men</td>
<td>43 ± 13</td>
</tr>
<tr>
<td>$\Delta$DBP, mmHg</td>
<td></td>
</tr>
<tr>
<td>Women, EF</td>
<td>16 ± 6*</td>
</tr>
<tr>
<td>Women, ML</td>
<td>12 ± 7*</td>
</tr>
<tr>
<td>Men</td>
<td>29 ± 6</td>
</tr>
<tr>
<td>$\Delta$MSNA-BF, bursts/min</td>
<td></td>
</tr>
<tr>
<td>Women, EF</td>
<td>18 ± 7*</td>
</tr>
<tr>
<td>Women, ML</td>
<td>20 ± 12*</td>
</tr>
<tr>
<td>Men</td>
<td>30 ± 7</td>
</tr>
<tr>
<td>$\Delta$MSNA-BI, bursts/100 heart beats</td>
<td></td>
</tr>
<tr>
<td>Women, EF</td>
<td>20 ± 10</td>
</tr>
<tr>
<td>Women, ML</td>
<td>24 ± 16</td>
</tr>
<tr>
<td>Men</td>
<td>29 ± 7</td>
</tr>
<tr>
<td>$\Delta$Total activity, a.u./min</td>
<td></td>
</tr>
<tr>
<td>Women, EF</td>
<td>632 ± 418*</td>
</tr>
<tr>
<td>Women, ML</td>
<td>598 ± 342*</td>
</tr>
<tr>
<td>Men</td>
<td>1025 ± 416</td>
</tr>
</tbody>
</table>

All values are the differences from baseline, means ± SD. PECA, postexercise circulatory arrest; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MSNA, muscle sympathetic nerve activity; BF, burst frequency; BL, burst incidence; a.u., arbitrary units. *Difference from men within stage, $P < 0.05$. Peak for CPT was defined as: HR, 0.5 min; SBP and DBP, 1.5 min; MSNA, 1.5 min.
from the present study are that 1) women demonstrate attenuated BP and MSNA responses during static handgrip to fatigue and during PECA compared with men; 2) women and men demonstrate comparable increases in MSNA (ΔMSNA-BF and Δtotal activity) in response to a cold pressor stimulus; and 3) low vs. high sex hormone exposure does not influence the cardiovascular or vasomotor sympathetic responses to static handgrip exercise or to the CPT in women.

The hypothesis that women would demonstrate a blunted sympathetic response during static handgrip to fatigue compared with the men; however, our results do not support the hypothesis that the high sex hormone phase results in further blunting of sympathetic responses to either static handgrip exercise or the CPT in the women.
We found that women demonstrated a similar contraction-induced peak HR during static handgrip to fatigue. Since this occurred with a concomitantly lower BP and vasomotor sympathetic response that persisted during PECA, when the contribution of central command and the stimulation of group III afferents was removed, it indicates that the disparate responses between the sexes are not likely due to the contribution of central command or the mechanoreflex. Moreover, it has been previously shown that central command contributes little to the rise in MSNA during static handgrip exercise (38). Since women and men had similar vasomotor sympathetic responses during the CPT, a nonexercise pressor stimulus, central processing and the efferent arm of the sympathetic nervous system are assumed to be comparably intact between the two groups.

Contributions of the Mechanoreceptor and Metaboreceptor During Static Exercise

The separate contributions of the mechanoreceptor and metaboreceptor during static exercise are difficult to assess. Mechanical deformation stimulates group III afferents and metabolites stimulate group IV afferents (20), both of which occur during static handgrip. The size of the active muscle mass has been thought to be a potential contributor to the magnitude of the increase in MSNA (29). For example, Seals (29) demonstrated that isometric handgrip evoked a larger increase in MSNA compared with isometric abduction of the first dorsal interosseus of the hand in the same subject. It is difficult, however, to extrapolate the findings of Seals (29) to those of intersubject differences. That is, do the men have higher MSNA during static exercise simply because a larger muscle mass is engaged? Ettinger et al. (6) addressed this issue by matching the sexes for anthropometric variables, as well as MVC (adductor pollicus) and time to fatigue, showing that women still had an attenuated MSNA response. Taken together, these studies suggest that activation of a larger muscle mass is associated with greater intrasubject increases in MSNA but does not necessarily explain intersubject differences. When size discrepancies are accounted for, there still remains a sex difference in the neural response to static exercise, which suggests the metaboreflex may be a larger contributor to the increase in MSNA and BP than the mechanoreflex.

Our findings are consistent with others who showed 1) baseline MSNA was comparable between the sexes (3, 6, 10, 11); 2) the low and high hormone phases of the menstrual cycle did not influence baseline MSNA (2, 10, 22, 23); and 3) women had a smaller change in MSNA from baseline during circulatory arrest after exercise (6). We interpret these findings as women demonstrating a reduced metaboreceptor response, which is independent of exposure to low or high sex hormone concentrations. Indeed, others have previously found, using [31p]-nuclear magnetic resonance spectroscopy, that women had lower concentrations of H/PO4 and H2PO4/PO3 in the muscle (6); H+ and H2PO4 have been positively associated with increases in MSNA (33, 36).

Cellular metabolite concentration should be related to the net effect of production and clearance, which is influenced by muscle fiber type. Saito (28) showed that static exercise performed in muscle groups of differing fiber type composition (very low type II → high type II) elicited dissimilar increases in MSNA. For example, forearm (high type II) static exercise...
elicited the largest increase in MSNA compared with the soleus (very low type II) (28), suggesting that type II fibers are associated with greater production and/or a decrease in clearance of metabolic byproducts compared with type I fibers. Indeed, animal studies have shown that lactate uptake is higher in type I fibers compared with type II fibers (19). These findings imply that fiber type distribution may vary between the sexes. In fact, human studies of biopsied vastus lateralis muscles have confirmed this hypothesis (32). Simoneau and Bouchard (32) studied biopsies of 270 healthy sedentary individuals (126 women, 144 men), reporting that while large interindividual differences exist, on the average women had a significantly higher percentage of type I fiber distribution. Taken together, these studies indicate that women have a higher proportion of type I fibers in the vastus lateralis, which may also be true of other muscle beds. The smaller proportion of type II fibers may lead to lower production of metabolites and the greater proportion of type I fibers may increase their capacity to buffer the metabolites, which may result in a smaller MSNA response in women during static exercise.

Influence of Sex Hormones on Exercise Pressor Reflex

Ettinger et al. (7) demonstrated that the estrogen fluctuations throughout the menstrual cycle did not influence baseline (resting) MSNA but did influence the response to static handgrip exercise. They showed that the increase in MSNA was attenuated during the high estrogen phase with unopposed progesterone (7). We were unable to replicate their finding; however, our study was consistent with another group that examined MSNA during ischemic, rhythmic handgrip exercise during the EF and ML phases of the menstrual cycle (25). Thus, one possible explanation for the disparate findings between our study and Ettinger et al. (7) could be related to the contribution of progesterone. Ettinger et al. (7) compared days 1–4 (EF) to days 10–12 (preovulatory) when estrogen, but not progesterone, was different. We compared days 1–4 (EF) to days 19–22 (ML) or during the low hormone phase and the high hormone phase for both estrogen and progesterone. The role of progesterone in cardiovascular control is not well defined and no consensus exists. However, the interaction of estrogen and progesterone is important as premenopausal women are exposed to both during the course of the menstrual cycle, where neither acts in true isolation. Thus, based on the differences between these studies (7, 25) and ours, it appears that the presence of progesterone may alter clearance of metabolic byproducts. We also cannot leave out the possibility that differences in experimental design (handgrip to fatigue vs. terminating handgrip at 2 min) and/or data analysis played a role in these observed differences.

Despite the large fluctuations in both estrogen and progesterone throughout the menstrual cycle, the response of the women remained similar between the low hormone and high hormone phases of the cycle in our study. Thus, findings from our study indicate that the acute alterations in sex hormones in women do not alter the cardiovascular and vasomotor sympathetic activity responses during static handgrip exercise. This does not exclude the long-term effects of cyclical exposure to estrogen and/or progesterone, which may contribute to the overall sex differences in the exercise pressor reflex.

Sex Differences in BP Responsiveness During the CPT

It is worth noting that the women demonstrated reduced DBP responses to the CPT compared with the men, despite similarities in MSNA. We, however, did not find sex differences in vascular transduction or differences between the low and high hormone phases of the menstrual cycle, which is consistent with others that have shown no difference between the EF and ML phases (25). Certainly there are other factors to consider that influence vascular tone and BP responsiveness. For example, it has been reported that women have greater β2-adrenergic sensitivity (21). Additionally, DBP does not differentiate the degree of vasoconstriction in beds like the splanchnic and renal circulations but only provides an overall assessment of total peripheral resistance. Therefore, it is possible that MSNA alone (i.e., the skeletal muscle bed) does not reflect the activity of other circulations.

Limitations

There are at least four limitations in our study. First, we did not assess the separate roles of estrogen and progestrone by measuring responses in the late-follicular phase (high estrogen/low progesterone). Second, we cannot ignore that men produced a higher absolute force than women during static handgrip exercise. However, Seals (30) posited that at fatigue sympathetic outflow is independent of the level of force (>20% of MVC); therefore, having the subjects perform handgrip to fatigue served as a way of normalizing potential differences between the sexes. Third, we did not measure metabolic byproducts during handgrip and PECA in our subjects. This, however, does not change the overall finding that a sex difference exists in cardiovascular and neural responses during PECA, demonstrating that women have a blunted metaboreflex response. Fourth, we did not assess the interaction of the metaboreflex and the arterial baroreflex in the present study. Some studies (5, 16) have suggested that during PECA there is an increase in baroreflex sensitivity. We cannot reject the possibility that baroreflex sensitivity was altered differently between the women and men during PECA in the present study. However, Cui et al. (5) reported that the metaboreflex is more powerful in increasing MSNA than any baroreflex-mediated suppression of MSNA. During pharmacologic manipulation (bolus injection of sodium nitroprusside followed by phenylephrine) of BP, and, therefore, MSNA during PECA, Cui et al. (5) found that MSNA was still significantly higher than baseline during the phenylephrine portion of the maneuver. Yet, in the nonexercise control trial of their study, MSNA was suppressed, though not statistically significant, compared with baseline (5). Thus, it is not likely that the contribution of the metaboreflex changes our findings. We acknowledge, however, that whether baroreflex sensitivity was differently altered during PECA between the two groups remains a separate and testable hypothesis, which was not the primary focus of this paper.

Perspectives and Significance

BP reactivity is one predictor for the future development of hypertension in young healthy individuals. Exposure to both estrogen and progesterone seem to confer a degree of cardioprotection in young premenopausal women. Indeed, premeno-
pausal women demonstrate lower resting BP and lower incidence of hypertension. Based on these findings, we surmise that this cardioprotection will be lost during menopause and that BP reactivity will be comparable or even greater in elderly women when the incidence of hypertension and cardiovascular disease is higher than in men (39).

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GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

REFERENCES