Chronic physical activity mitigates cerebral hypoperfusion during central hypovolemia in elderly humans

Kevin Formes,1,2 Peizhen Zhang,1,3 Nancy Tierney,2 Frederick Schaller,2 and Xiangrong Shi1

Departments of 1Integrative Physiology and 2Internal Medicine, University of North Texas Health Science Center, Fort Worth, Texas; and 3Division of Sports Medicine, Beijing Sport University, Beijing, China

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Formes K, Zhang P, Tierney N, Schaller F, Shi X. Chronic physical activity mitigates cerebral hypoperfusion during central hypovolemia in elderly humans. Am J Physiol Heart Circ Physiol 298: H1029–H1037, 2010. First published December 31, 2009; doi:10.1152/ajpheart.00662.2009.—This study sought to test the hypothesis that orthostasis-induced cerebral hypoperfusion would be less severe in physically active elderly humans (ACT group) than in sedentary elderly humans (SED group). The peak O2 uptake of 10 SED (67.1 ± 1.4 yr) and 9 ACT (68.0 ± 1.1 yr) volunteers was determined by a graded cycling exercise test (22.1 ± 1.2 vs 35.8 ± 1.3 ml·min⁻¹·kg⁻¹, P < 0.01). Baseline mean arterial pressure (MAP; tonometry) and middle cerebral arterial blood flow velocity (V_{MCA}: transcranial Doppler) were similar between the groups (SED vs. ACT group: 91 ± 3 vs. 87 ± 3 mmHg and 54.9 ± 2.3 vs. 57.8 ± 3.2 cm/s, respectively), whereas heart rate was higher and stroke volume (bi-impedance) was smaller in the SED group than in the ACT group. Central hypovolemia during graded lower body negative pressure (LBNP) was larger (P < 0.01) in the ACT group than in the SED group. However, the slope of V_{MCA}/LBNP was smaller (P < 0.05) in the ACT group (0.159 ± 0.016 cm/s/Torr) than in the SED group (0.211 ± 0.008 cm/s/Torr). During LBNP, the SED group had a greater augmentation of cerebral vasomotor tone (P < 0.05) and hypocapnia (P < 0.001) compared with the ACT group. Baseline MAP variability and V_{MCA} variability were significantly smaller in the SED group than in the ACT group, i.e., 0.49 ± 0.07 vs. 1.04 ± 0.16 (mmHg)² and 1.06 ± 0.19 vs. 4.24 ± 1.59 (cm/s)², respectively. However, transfer function gain, coherence, and phase between MAP and V_{MCA} signals (Welch spectral estimator) from 0.08–0.18 Hz were not different between SED (1.41 ± 0.18 cm·s⁻¹·mmHg⁻¹, 0.63 ± 0.06 units, and 38.03 ± 6.57°) and ACT (1.65 ± 0.44 cm·s⁻¹·mmHg⁻¹, 0.56 ± 0.05 units, and 48.55 ± 11.84°) groups. We conclude that a physically active lifestyle improves the intrinsic mechanism of cerebral autoregulation and helps mitigate cerebral hypoperfusion during central hypovolemia in healthy elderly adults.

METHODS

Subjects. Ten healthy, average fit sedentary (6 men and 4 women; SED group) and 9 physically active (6 men and 3 women; ACT group) elderly adults voluntarily participated in the study after giving their informed consent and passing a physical examination (see Table 1 for their physical characteristics). Although group age was not different between the sedentary (67.1 ± 1.4 yr) and physically active (68.0 ± 1.1 yr) subjects, body mass index was greater (P < 0.05) in the SED group (29.5 ± 1.6) than in the ACT group (22.9 ± 0.7). The study protocol was approved by the Institutional Review Board for the Protection of Human Subjects of the University of North Texas Health Science Center (Fort Worth, TX). All subjects were clinically confirmed to be free of cardiovascular, metabolic, renal, and pulmonary diseases and symptoms before the exercise stress test. Before the medical examination, ~10% of subjects who had given their consent and medical/health history were excluded from the study because of taking medications, such as adrenergic blockers or diuretics, which could directly interfere with arterial baroreflex function or cardiovas-
Lifestyle, duration of exercise training, type of physical exercise, exercise frequency, and time were reported by the subjects. 70% of healthy elderly subjects were able to produce a desirable familiarize with themselves with the experimental procedures and as physically inactive or untrained (see Table 1). Before the experiment, each subject’s heart rate under the supine resting condition was selected for transfer function analysis. The position and angle of the TCD probe was fixed to the head using a custom-made ring held by a Velcro band throughout the test as previously described (13). Systematic arterial O2 saturation (Sao2) was measured by an arterial pulse oximeter (OX100C, Biopac). The fraction of end-tidal CO2 (PetCO2) in a subgroup of the SED (n = 8) and ACT (n = 7) groups was continuously monitored via a nasal cannula using a mass spectrometer (1100 Medical Gas Analyzer, Perkin-Elmer, St. Louis, MO). PetCO2 was calculated from the product of ambient barometric pressure (corrected with vapor pressure) and FETCO2. All these analog data were digitized at 400 Hz and continuously monitored by a computer interfaced with a data-acquisition system (Biopac). Total peripheral resistance (TPR), forearm vascular resistance (FVR), and the index of cerebral vascular resistance (CVR) were derived offline from the ratios of MAP to Q, MAP to FBF, and MAP to VMCA, respectively.

Procedures. The experiment was carried out with the subject’s lower body supported in an airtight LBNP box in the supine position at a room temperature of 24–25°C. After ≥20 min of supine rest, the subject’s baseline HR, SV, ABP, VMCA, RCo2, Sao2, and PetCO2 data were continuously recorded for 6 min; meanwhile, four to five FBF curves were collected after ~45 s of the wrist cuff being inflated and maintained at ~200 mmHg to arrest the circulation of the hand. After the baseline data collection, graded LBNPs of 50 Torr were continuously applied, and each grade of LBNP was maintained for 6 min. Two SED subjects and 1 ACT subject did not complete the whole LBNP ramp because of the appearance of presyncope. Cardiovascular variables and PetCO2 were continuously monitored during LBNP.

Data analyses. A section of 5-min continuous VMCA and MAP data under the supine resting condition was selected for transfer function analysis using the Welch spectral estimator (35). The transfer function between MAP-VMCA signals [i.e., H(f)] was computed from the cross-spectrum (CS) between MAP-VMCA variabilities [CS(MAP,VMCA)(f)] and autospectrum (AS) VMCA variability [AS(VMCA)(f)] as follows: H(f) = [CS(MAP,VMCA)(f)]/[AS(VMCA)(f)]. The real and imaginary components of the power spectrum are the real and imaginary parts of the transfer function. The magnitude of the transfer function is the ratio of the power spectrum of the MAP-VMCA variabilities to the power spectrum of the VMCA variability.
of $H(f)$ [$H_a(f)$ and $H_b(f)$, respectively] were used to calculate the magnitude or gain, i.e., $H(f)_G = |H_a(f)|^2 + |H_b(f)|^2$. The time relationship or phase [$\theta(f)$] between MAP and MCA signals was calculated as follows: $\theta(f) = \arctan[H_a(f)/H_b(f)]$. The coherence [$C(f)$] was calculated as follows: $C(f) = |AS_{MAPVMCA}(f)/AS_{VMCA}(f)|$, where $AS_{VMCA}$ is the autospectrum of MCA variability. Transfer function magnitude, phase, and coherence between the 0.08- and 0.18-Hz spectrum (where the group average coherence was $\approx 0.5$) along with MCA variability and MAP variability were extracted and compared between the groups. This spectral range (i.e., 0.08–0.18 Hz) of the transfer function data between MAP and MCA variabilities is below normal breathing frequency and has been selected for the assessment of dynamic cerebral autoregulation (3, 51, 53). In addition, baseline low-frequency (LF; 0.05–0.15 Hz) and high-frequency (HF; 0.16–0.40 Hz) HR variability were analyzed as described in our previous studies (8, 49).

Differences in baseline data between the groups were determined by the two-tailed $t$-test with two independent samples. Two-way ANOVA for repeated measures was applied to determine the significance of LBNP and fitness factors on cardiovascular and respiratory responses. Assessment of the relative changes (i.e., the responses) allowed us to minimize the influence of individual variance between or within the groups and to normalize the responses with different units. Post hoc analysis with Tukey’s option was applied when the major factor reached significance (i.e., $P$ values of $\leq 0.05$). Simple linear regression was applied for assessment of the relationship (i.e., slope) between two variables. A general linear model procedure was applied for the comparison of the slopes between SED and ACT subjects and for the assessment of the interaction between LBNP and fitness factors. All data are reported as group means $\pm$ SE. Statistical Analysis System softward (Cary, NC) was applied for statistical analyses.

**RESULTS**

**Baseline data.** Baseline ABP was not significantly different between the two elderly groups. However, HR was lower ($P = 0.010$) and SV was greater ($P = 0.011$) in ACT subjects than in SED subjects (Table 2). Baseline $V_{MCA}$ and $V_{CO2}$ were statistically similar between SED and ACT groups. The breathing rate at rest was faster ($P = 0.025$) in SED subjects than in ACT subjects, whereas baseline $P_{T_{CO2}}$ was not significantly different between the two independent samples.

<table>
<thead>
<tr>
<th>Table 2. Baseline physiological characteristics</th>
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<td>Variables</td>
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<tr>
<td>Heart rate, beats/min</td>
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<td>Stroke volume, ml</td>
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<td>Cardiac output, l/min</td>
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<td>Systolic blood pressure, mmHg</td>
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<td>Diastolic blood pressure, mmHg</td>
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<td>Forearm blood flow, ml·100$^{-1}$·g$^{-1}$·min$^{-1}$</td>
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<td>Forearm vascular resistance, units</td>
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<td>Middle cerebral artery blood flow velocity, cm/s</td>
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<td>Cerebral vascular resistance, units</td>
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<td>Regional cerebral tissue oxygenation, %</td>
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<td>End-tidal $P_{CO2}$, mmHg</td>
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<td>Respiratory rate, cycles</td>
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Values are means $\pm$ SE. $P$ values were the outcome of a $t$-test with two independent samples.
LBNP effects. In both SED and ACT groups, SV was progressively decreased \((P = 0.0001)\) with graded LBNP (Fig. 2), indicating central hypovolemia. HR was progressive increased above the LBNP of \(-20\) Torr as a result of unloading arterial baroreceptors. Decreases in \(Q\), \(V_{MCA}\), and FBF were significantly \((P < 0.05)\) correlated with LBNP or central hypovolemia, which were associated with significant increases in TPR, FVR, and CVR, respectively, in both subject groups (Fig. 3). However, LBNP-elicited central hypovolemia did not cause significant changes in MAP \((P > 0.05)\) in either group (Fig. 2), which was likely compensated for by a vasoconstriction stimulated by the baroreflex-mediated sympathoexcitation (22, 36). Neither systolic blood pressure nor diastolic blood pressure was statistically affected by LBNP. Although \(Sao_2\) was not significantly altered \((P > 0.05)\), \(Rco_2\) was significantly decreased \((P < 0.05)\) across both SED and ACT groups (Fig. 2). Hypocapnia was observed, as indicated by a progressive decrease in \(PETco_2\) during graded LBNP (Fig. 4). Significant decreases in \(PETco_2\) appeared at \(-20\) Torr of LBNP in both SED \((-1.57 \pm 0.44\) mmHg) and ACT \((-1.36 \pm 0.39\) mmHg) groups. The decreases in \(PETco_2\) were augmented with further increases in LBNP, e.g., \(-4.07 \pm 1.29\) and \(-2.23 \pm 0.64\) mmHg at \(-50\) Torr in SED and ACT subjects, respectively.

Fitness effects. Decreases in SV during LBNP were significantly more severe in the ACT group than in the SED group (Fig. 2), whereas the tachycardiac responses were significantly greater in the ACT group than in the SED group, indicating sensitized baroreflex control of HR in the exercise-trained elderly adults. The slopes of \(Q/LBNP\) and \(TPR/LBNP\) were not different between SED and ACT subjects. However, the rate of decreases in \(V_{MCA}\) per unit change in LBNP were greater \((P = 0.025)\) in SED subjects (slope: \(0.375 \pm 0.014%)/\)Torr, \(R^2 = 0.99\) than in ACT subjects (slope: \(0.289 \pm 0.029%)/\)Torr, \(R^2 = 0.95\). In addition, the rate of increases in CVR per unit change in LBNP were significantly greater \((P = 0.039)\) in SED subjects (slope: \(-0.449 \pm 0.057%)/\)Torr, \(R^2 = 0.90\) than in ACT subjects (slope: \(-0.275 \pm 0.046%)/\)Torr, \(R^2 = 0.88\)). Neither the slopes of FBF/LBNP nor the slopes of FVR/LBNP were statistically different between SED and ACT subjects (see Fig. 3).

During graded LBNP, the rate of decreases in \(PETco_2\), (i.e., the slope) was significantly greater \((P = 0.0008)\) in SED subjects \((0.088 \pm 0.008\) mmHg/Torr, \(R^2 = 0.96)\) than in ACT subjects \((0.039 \pm 0.006\) mmHg/Torr, \(R^2 = 0.88)\); see Fig. 4). However, the slopes of CVR and \(V_{MCA}\) in response to \(PETco_2\), during LBNP were not significantly different between the two groups (Fig. 5).

Although the slopes of \(\%ΔFVR/ΔTPR\) during graded LBNP were not significantly different \((P = 0.166)\) between SED \((1.83 \pm 0.18, R^2 = 0.95)\) and ACT \((1.49 \pm 0.15, R^2 = 0.95)\) groups (Fig. 6, top left), the rate of augmented CVR in terms of per unit increase in TPR (i.e., the slope of \(\%ΔCVR/ΔTPR\) was significantly greater \((P = 0.0476)\) in SED subjects \((0.84 \pm 0.14, R^2 = 0.88)\) than in ACT subjects \((0.45 \pm 0.11, R^2 = 0.77)\); Fig. 6, bottom left). The slopes of \(\%ΔFBB/ΔQ\) (Fig. 6, top right) and \(\%ΔV_{MCA}/ΔQ\) (Fig. 6, bottom right) tended to be greater in the SED group than in the ACT group.

DISCUSSION

The present study provides two novel findings. First, the cerebral hypoperfusion that occurred during mild to moderate LBNP was less severe in ACT elderly subjects compared with
SED elderly subjects. This finding appears to suggest that an enhanced cardiovascular-respiratory fitness of healthy seniors resulting from a physically active lifestyle or chronic physical activity may help protect the brain against hypoperfusion under orthostatic stress. Second, baseline MAP variability and V_{MCA} variability were significantly smaller in SED elderly subjects than ACT elderly subjects, although the transfer function magnitude or gain between MAP and V_{MCA} signals was not different between the two groups under the resting condition.

During orthostatic challenge, there are three factors likely involved in a subsequent cerebral hypoperfusion or reduction of cerebral blood flow. First, the reduction of venous return and resulting reduction of Q restrict the systemic availability of circulating blood flow (5, 13, 18, 26). Second, baroreflex-mediated sympathoexcitation may increase cerebral vasomotor tone along with an augmented TPR (2, 13, 21, 26). This neurogenically augmented CVR would reduce V_{MCA} in the presence of stable or falling MAP. Third, hypocapnic hyperventilation, as indicated by a decrease in PETCO2, stimulates cerebral vasoconstriction (21, 24, 38). This chemogenically augmented CVR would also cause a diminution of cerebral blood flow.

Since the LBNP-induced reductions of SV and Q tended to be greater in the ACT group than in the SED group in the present study, the altered systemic flow availability was not likely a responsible mechanism for the difference in cerebral hypoperfusion observed between the two groups. During graded LBNP, TPR appeared to be similarly augmented in both
SED and ACT elderly subjects. These data suggested that the sympathoexcitation-mediated augmentation of total peripheral vasomotor tone was comparable between the groups. Therefore, a difference in sympathoexcitation and its neurogenic influence during LBNP was unlikely to be the factor responsible for the difference in cerebral hypoperfusion between the groups. However, in terms of per unit increase in TPR, the rate of the augmented CVR during LBNP was significantly greater in SED than in ACT subjects (Fig. 6). These data implied that the function of cerebral autoregulation could be diminished in the SED group and that the cerebral regional mechanism could be less effective to protect cerebral perfusion against the augmented cerebral vasomotor tone during LBNP. Alternatively, cerebral vasomotor tone could have been stimulated by a greater chemogenic influence (i.e., decrease in PETCO2) in the SED group during LBNP.

The present study indicated that the decrease of PETCO2 or LBNP-elicited hypocapnia was greater in SED than in ACT subjects (see Fig. 4). Hypocapnia manifested by decreases in PETCO2 or arterial PCO2 during orthostasis has been reportedly occurred during LBNP and whether this adaption affected the subjects differently based on fitness level are not known. Since graded hypocapnia occurred with progressive increases in LBNP intensity (Fig. 4), which was significantly correlated with the changes in CVR or VMCA in both groups (Fig. 5), our data suggested that hypocapnia remained potent on cerebral vasomotor tone in the present experimental setting. Based on the data that the diminished PETCO2 was significantly smaller in the ACT group compared with the SED group, we suggested that a difference in hypocapnia elicited by LBNP was likely a mechanism responsible for the different cerebral hypoperfusion between SED and ACT groups, in addition to the function of cerebral autoregulation and the reduction of venous return. Previously, Ide et al. (16) observed a peak slope of VMCA/PETCO2 of ~2.5%/mmHg during hypocapnia-elicited changes in VMCA without central hypovolemia, which was much smaller than the slopes of VMCA/PETCO2 in both the SED (4.3%/mmHg) and ACT (6.2%/mmHg) elderly groups in the present study. Collectively, these data implied that a portion of the ~50% decrease in VMCA or increase in CVR during LBNP in the present study could be explained by central hypovolemia or its reflex sympathoexcitation. An alternative explanation for the difference in cerebral hypoperfusion between the two elderly groups during LBNP in the present study may involve a cerebral regional or intrinsic mechanism that differently counteracts the augmentation of cerebral vasomotor tone induced by hypocapnia or sympathoexcitation. Evidence that this cerebral regional mechanism was effective is manifested by a smaller increase in CVR compared with TPR in both SED and ACT subjects during LBNP (Fig. 6) with the presence of hyperventilation-elicited hypocapnia. However, in terms of per unit increase in TPR, the rate of augmentation of CVR was significantly smaller in ACT than in SED subjects, indicating a potential difference in the activation of a cerebral regional mechanism.

The transfer function magnitude between beat-to-beat MAP and VMCA variabilities has been considered as a gain of dynamic cerebral autoregulation (28, 40, 52, 53). Under the supine resting condition, there were no differences in transfer function gains between SED and ACT groups (Fig. 1). However, the beat-to-beat oscillations in both MAP and VMCA spectral power were significantly smaller in the SED group compared with the ACT group in the present study. These data suggested that the beat-to-beat MAP variability and VMCA variability of the SED group oscillated within a much narrower range, although the gain or sensitivity of the dynamic cerebral autoregulation at rest was not different between the two elderly groups (Fig. 1). The mechanism for a smaller baseline MAP variability observed in the SED group is not fully understood. It may be related to a greater stiffness of arterial blood vessels associated with aging, which appears to be favorably alleviated or reversed after chronic exercise training in older adults (6, 37, 46). Another possibility for the smaller MAP variability in the SED group may be related to a diminished HR variability,
which was significantly smaller in the SED group compared with their ACT cohort. Although ABP variability precedes HR variability, the latter may also conversely exert its influence on beat-to-beat ABP oscillation in the closed cardiovascular system when MAP is less affected by sympathetic nerve activity under the supine resting condition. This postulation seems to be supported by the observation that ABP variability is significantly diminished after the impairment of HR variability with vagal-cardiac blockade using atropine or glycopyrrolate (49).

Cerebral hypoperfusion is one mechanism responsible for orthostatic intolerance (14, 15, 20, 26, 29, 48). For example, patients with idiopathic orthostatic intolerance show a greater decrease in $V_{\text{MCA}}$ and a greater increase in CVR compared with age- and sex-matched healthy adults during graded orthostatic stress simulated by head-up tilt (20). The better maintained cerebral perfusion observed in the elderly ACT group compared with the elderly SED cohort in the present study seems to be contrary to the belief that “trained man can run, but they cannot stand” (12). More incidence of orthostatic intolerance in high-fit younger subjects has been observed compared with their age-matched healthy, average-fit counterparts, which has been reported to be related to a greater cardiac compliance (27) that compromises SV output (25) and a diminished baroreflex sensitivity that compromises tachycardiac and vasoconstrictive responses (33). As a result, the fitness-related cardiovascular alternations in younger athletes may compromise their orthostatic tolerance and cerebral perfusion during orthostatic stress. However, the present study (Fig. 2) and our previous data (44) have indicated that baroreflex function appeared to be enhanced in elderly subjects with a physically active lifestyle. This observation was opposite to the difference in arterial baroreflex sensitivity between younger high-fit and average-fit subjects, which has been shown to be diminished after exercise training based on both cross-sectional and longitudinal comparisons (31, 33, 45). Although left ventricular compliance is greater in master athletes than in healthy sedentary seniors, a difference in compliance is not distinguishable between elderly high-fit and young average-fit subjects (3). Collectively, these data suggest that exercise training prevents the impact of physical fitness on the regulation of cerebral blood flow during orthostasis is age specific. Chronic physical activity counteracts secondary aging and provides more protection against cerebral hypoperfusion during orthostatic challenge in elderly people. However, a previous study (9) did not detect a fitness-related difference in $V_{\text{MCA}}$ during steady-state LBNP in healthy elderly subjects. An important factor in this discrepancy is that $V_{\text{MCA}}$ was constantly maintained during mild to moderate LBNP in both old fit and old unfit subjects in the previous study (9), whereas $V_{\text{MCA}}$ was progressively decreased with central hypovolemia in both SED and ACT subjects in the present study (Fig. 2). Our data suggested that the intrinsic mechanism of cerebral autoregulation could be diminished in the SED group compared with their ACT cohort, indicating a diminished function of cerebral autoregulation during central hypovolemia.

The present study has some potentially important implications. Habitual exercise not only provides a beneficial influence on overall cardiovascular conditioning but also mitigates cerebral hypoperfusion in elderly adults during an orthostatic challenge. Physiologically, this provides a margin of safety against orthostatic intolerance. Nonetheless, the present study was limited to a cross-sectional comparison. A longitudinally designed study is needed to more definitively distinguish the impact of secondary aging from primary aging on cerebral function.
hypoperfusion during central hypovolemia. Also, only mild to moderate LBNP was applied to simulate orthostasis in the present study, which could not produce the true orthostatic impact on venous return (or ventilation) and orthostatic intolerance. Another limitation of the study was that the change in $P_{a}CO_2$ was determined for hypocapnia during LBNP. Although this noninvasive method was commonly applied in previous studies (1, 11, 16) and highly correlated with arterial blood $CO_2$ (18, 19, 39), direct systemic hypocapnia may be overestimated by $P_{a}CO_2$ (18, 38).

In conclusion, improved physical fitness resulting from a physically active lifestyle or chronic physical activity in elderly adults mitigates cerebral vasoconstriction and hypoperfusion during central hypovolemia. Our data indicate that the intrinsic mechanism of cerebral autoregulation may be improved, along with the sensitized arterial baroreflex control of HR, in the physically active elderly compared with the sedentary elderly adults. This adaptive change may help prevent orthostatic intolerance in physically active elderly people, which is different from the observation made in their younger counterparts.

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DISCLOSURES

No conflicts of interest are declared by the author(s).

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