Ethnic differences in resistance artery contractility of normotensive pregnant women

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Brewster LM, Taherzadeh Z, Volger S, Clark JF, Rolf T, Wolf H, VanBavel E, van Montfrans GA. Ethnic differences in resistance artery contractility of normotensive pregnant women. Am J Physiol Heart Circ Physiol 299: H431–H436, 2010. First published May 28, 2010; doi:10.1152/ajpheart.00919.2009.—Black women are at a greater risk to develop hypertension during pregnancy, with a 4.5 times higher rate of fatal preeclampsia than white women. Therefore, it is important to identify factors that may affect this risk. Our group previously proposed that high activity of the central regulatory enzyme of energy metabolism, creatine kinase (CK), may increase ATP-buffering capacity and lead to enhanced vascular contractility and reduced nitric oxide bioavailability. Therefore, we assessed microvascular contractility characteristics in isolated resistance arteries from self-defined black and white normotensive pregnant women using a Mulvany-Halpern myograph. Additionally, morphology was assessed with electron microscopy. Resistance-sized arteries obtained from omentum donated during cesarean sections (11 black women and 20 white women, mean age: 34 yr) studied in series showed similar morphology but significantly greater maximum contractions to norepinephrine (10−5 M) in blacks [14.0 mN (1.8 SE)] compared with whites [8.9 mN (1.4 SE), P = 0.02]. Furthermore, we found greater residual contractility after the specific CK inhibitor dinitrofluorobenzene (10−6 M) in black women [55% (6 SE)] compared with white women [28% (4 SE), P = 0.001] and attenuated vasodilation after bradykinin (10−5 M) in black women [103% (6 SE)] compared with white women [84% (5 SE), P = 0.023], whereas responses to sodium nitroprusside (10−4 M) and amlodipine (10−6 M) were similar. We conclude that compared with white women, normotensive pregnant black women display greater resistance artery contractility and evidence of higher vascular CK activity with attenuated nitric oxide synthesis. These findings in normotensives may imply that the black population is at risk for a further incline in pregnancy-related hypertensive disorders.

pregnancy; blood pressure; hypertension; preeclampsia; ethnic groups; nitric oxide; creatine kinase

There is an increasing trend in ethnic disparities in hypertensive diseases of pregnancy (9, 18, 23, 28, 35). All hypertensive disorders combined and preeclampsia are most often diagnosed in black women of all socioeconomic backgrounds studied (8.5% of pregnancies in black women compared with 5.5% in white women) (35). Furthermore, it has been estimated that black women have a 4.5 times greater rate of fatal preeclampsia or eclampsia than white women, accounting for most of the ethnic disparities in maternal mortality (23).

These observations are in accordance with the increasing black-white disparity in the prevalence of hypertension in the general population (5, 12, 16, 32). According to National Health and Nutrition Examination Survey data, the prevalence of hypertension in black adults increased from 35.8% in 1988–1994 to 40.1% in 1999–2004. In the same period, the prevalence among whites rose from 23.3% to 27.4% (12). Black women have been reported to have the steepest age gradient of all race/sex groups studied (16). In the age group of 30–39 yr, the prevalence of hypertension is 14.5% among black women versus 5.4% in white women (12). These trends translate into disparities in the prevalence of hypertension during pregnancy, as more black women enter pregnancy with preexisting hypertension.

Because of the greater occurrence of obstetric hypertension and preeclampsia in black women, it is important to further identify factors that affect this risk. In general, black women have been reported to be more socioeconomically disadvantaged and access healthcare less often and later (35), but very few studies have attempted to uncover the biological basis of these racial differences in hypertension-related maternal and neonatal morbidity and mortality (27). Reduced nitric oxide (NO) bioavailability has been recognized as a hallmark of preeclampsia (27), and low NO bioavailability has been reported in nonpregnant black people (27), but, to our knowledge, ethnic differences in microvascular contractility and NO-dependent responses during pregnancy have not been previously studied. Our group (3, 5) previously proposed that high activity of the central regulatory enzyme of energy metabolism, creatine kinase (CK; EC 2.7.3.2), increases the ATP-buffering capacity for muscle contractility. This may contribute to the enhanced vascular contractility in subjects with high CK. In addition, the high creatine synthesis that accompanies high CK activity (21) may attenuate NO bioavailability, since creatine and NO-synthesizing enzymes compete for the common precursor L-arginine (3, 5). CK has been identified by our group (3, 5) previously proposed that high activity of the central regulatory enzyme of energy metabolism, creatine kinase (CK; EC 2.7.3.2), increases the ATP-buffering capacity for muscle contractility. This may contribute to the enhanced vascular contractility in subjects with high CK. In addition, the high creatine synthesis that accompanies high CK activity (21) may attenuate NO bioavailability, since creatine and NO-synthesizing enzymes compete for the common precursor L-arginine (3, 5). CK has been identified by our group (3, 5) as an independent risk factor for hypertension in the general population, with a 14-mmHg increase in systolic blood pressure per log CK increase. Black people in the general population have been found to have the highest CK levels (5) as an independent risk factor for hypertension in the general population (5, 12, 16, 32). According to National Health and Nutrition Examination Survey data, the prevalence of hypertension in black adults increased from 35.8% in 1988–1994 to 40.1% in 1999–2004. In the same period, the prevalence among whites rose from 23.3% to 27.4% (12). Black women have been reported to have the steepest age gradient of all race/sex groups studied (16). In the age group of 30–39 yr, the prevalence of hypertension is 14.5% among black women versus 5.4% in white women (12). These trends translate into disparities in the prevalence of hypertension during pregnancy, as more black women enter pregnancy with preexisting hypertension.

METHODS

Outcomes. The primary outcome was a difference in the maximum contractility of isolated resistance-sized arteries obtained from white

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H431

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Women undergoing a cesarean section at term under local anesthesia

Consecutive self-defined white and black normotensive pregnant women were enrolled in this study, which was approved by the Institutional Review Board.

Sample size calculation. Sample size calculations were based on the primary outcome. To our knowledge, there are no data on ethnic differences in vascular contractility responses in vitro. Therefore, we used observations of vascular contractility in isolated arteries from white and black patients, respectively (34) in white and black pregnant women, respectively (P value for the difference > 0.05).

Baseline Parameters | White Women | Black Women | Difference (P Value)
--- | --- | --- | ---

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>SD</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>34.4 ± 0.8</td>
<td>34.5 ± 1.6</td>
<td>0.93</td>
<td></td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td>39.3 ± 0.3</td>
<td>38.8 ± 0.7</td>
<td>0.55</td>
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</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.5 ± 1.2</td>
<td>27.7 ± 1.3</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>104.9 ± 2.9</td>
<td>105.9 ± 3.5</td>
<td>0.83</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>59.3 ± 1.8</td>
<td>63.1 ± 2.7</td>
<td>0.27</td>
<td></td>
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</tbody>
</table>

Values are means ± SE; n, no. of participants/group. BMI, body mass index at term, which was calculated as weight (in kg) divided by height (in m²). P values are two-sided.

Microvessel preparation and tension measurements. We performed the tests in multiple vessels obtained from consecutive patients at our clinic. We assessed different steps in the contractile process of resistance arteries [Fig. 1; modified from Brewster et al. (5)]. After maternal omental biopsy, performed immediately after delivery of the child, the omental fat pad sample was immediately placed into cold (4°C), oxygenated physiological salt solution (PSS) consisting of (in mmol/l) 118.2 NaCl, 24.8 NaHCO₃, 4.6 KCl, 1.2 KH₂PO₄, 1.2 MgSO₄, 2 CaCl₂, 0.26 EDTA, and 50 HEPES. Vessels were dissected under a microscope and cleaned of adherent adipose and connective tissues. Segments of resistance-sized arteries (~200–400 μm normalized internal diameter) were cut into 2-mm-long rings (1–4 rings, median: 2.5 mm/participant), which were mounted on 40-μm stainless steel wires in a Mulvany-Halpern myograph (Danish Myo Technology, Copenhagen, Denmark). The myograph bath contained PSS at 37°C bubbled with 5% CO₂ in O₂ to maintain a pH of 7.4. After 1 h of equilibration, passive tension and internal circumference characteristics were determined.

We included vessels that were able to generate active tension at least 50-mmHg equivalent pressure. Each ring was normalized and set to the optimal radius for active tension at 90% of the diameter of a passive vessel at a pressure of 100 mmHg [mean normalized diameters of 269 μm (95% confidence interval: 223–308) and 305 μm (95% confidence interval: 223–388)] in white and black patients, respectively (P value for the difference > 0.05).

Baseline characteristics of the participants

Table 1.

Efficacy virus infection, infectious hepatitis, and bleeding disorders. All participants gave written informed consent.

Intramural pathways in vascular smooth muscle contraction. This is a schematic representation of the main intracellular regulatory pathways of vascular smooth muscle contraction and mechanisms of action of vasodilators used in this study modified from Brewster et al. (5). Creatine kinase (CK) is colocalized with Ca²⁺-ATPase and myosin ATPase, and evidence suggests that the enzyme is also colocalized with myosin light chain kinase (MLCK) to rapidly supply these enzymes with ATP using creatine phosphate (create-P) (5, 10, 14). The guanidino compounds creatine and nitric oxide (NO) have a common precursor in L-arginine (37). NO, RhoA/Rho kinase, and Ca²⁺-dependent pathways are intracellular effectors of the blood pressure-regulating systems that converge on metabolic processes fueled by CK (5, 10, 14, 25, 29, 36, 37). Vascular contractile responses can be reduced through the direct inhibition of CK-dependent pathways or through the stimulation of NO-dependent pathways. Dinitrofluorobenzene (DNFB) is a specific and irreversible blocker of CK and is shown here to affect CK bound near the ATPases, but this inhibitor probably affects mitochondrial CK as well (38). The Ca²⁺ channel blocker amlodipine (CAB) has been reported to block the entry of Ca²⁺ in the cell as well as the outflow from the sarcoplasmic reticulum (SER) (34). NO-dependent pathways were stimulated in this study through NO donation by sodium nitroprusside (SNP) and through bradykinin-induced NO synthesis (24). MLCP, myosin light chain phosphatase.

and black women. An ethnic difference in contractility responses after the specific CK inhibitor dinitrofluorobenzene (DNFB) was the secondary outcome. Other outcomes included the effect of sodium nitroprusside (SNP), the Ca²⁺ channel blocker amlodipine, and bradykinin. Finally, we also assessed the effect of adenylate kinase (AK; EC 2.7.4.3) inhibition, the effect of a competitive inhibitor of NO synthase (NOS; EC 1.14.13.39), N⁶-nitro-L-arginine (L-NNA), active and passive tension relationships (as measures of the structural characteristics of the arteries), and morphology by electron microscopy.

Sample size calculation. Sample size calculations were based on the primary outcome. To our knowledge, there are no data on ethnic differences in vascular contractility responses in vitro. Therefore, we used observations of vascular contractility in isolated arteries from white and black pregnant women, respectively (34) in white and black pregnant women, respectively (P value for the difference > 0.05).

Maximum contractility was induced in the isolated arteries in duplicate with norepinephrine (10⁻⁵ M) in KCl (125 mM)-substituted PSS. After arteries had been washed and reequilibrated in PSS, a cumulative concentration-response curve, with a 3-min incubation time before each increment in concentration, was constructed for bradykinin (10⁻¹⁰–10⁻⁷ M), and passive and active diameter-tension relations were studied. In a further series of tests, SNP (10⁻⁹–10⁻⁴ M)-induced and amlodipine (10⁻⁸–10⁻⁶ M)-induced vasodilation were studied, and, finally, the irreversible CK blocker DNFB (10⁻⁷–10⁻⁶ M) was added. In a subset of patients, we used DNFB up to 10⁻⁵ M before the addition of the AK blocker P1,P5,di(adenosine-5')pentaphosphate (Ap5A) in concentrations of 10⁻⁶–10⁻⁵ M. AK serves as an alternative ATP-buffering system and catalyzes the following reaction: 2 ADP ↔ ATP + AMP (14). L-NNA was used at 10⁻⁵ M with 30 min of preincubation before the addition of norepinephrine. Stock solutions of reagents (except DNFB) were prepared fresh daily in distilled water and diluted serially for use in myograph baths. DNFB was prepared as a 10⁻⁴ M stock solution in DMSO and then further diluted in the myograph bath to give the appropriate final concentrations (final DMSO concentration: 0.5%). In preliminary experiments, we found that the concentration of 0.5% DMSO did not
cause any significant effect on vascular responses. All concentrations refer to final bath concentrations.

**Electron microscopy.** Segments of resistance-sized vessels (2 mm in length) were immediately placed in McDowell’s solution and refrigerated until fixation with 1% osmium tetroxide (Electron Microscopy Sciences, Hatfield, PA) and 1% lanthanum nitrate in water for 1 h at room temperature followed by 1% aqueous uranyl acetate for 1 h. Vessels were dehydrated through an alcohol sequence and embedded in Epon 812 resin. Sections of 1 μm were stained with Richardson’s stain. Areas of interest were selected, trimmed, and cut with a diamond knife. Sections of ~60 nM in thickness were stained with Reynolds lead citrate and uranyl acetate. Electron microscopic images were obtained with an EM420 transmission electron microscope (Philips, Eindhoven, The Netherlands) operating at 120 kV.

Anatomic measures were derived from the electron microscopic images using ImageJ (ImageJ version 1.38, National Institutes of Health, Bethesda, MD; http://rsbweb.nih.gov/ij/). Media thickness was defined as the distance from the inner border of the internal elastic lamina to the outer border of the smooth muscle layer. The proportion of smooth muscle cells and collagen within the media was quantified by manually tracking the respective areas. Data from five to seven different locations in each image and five to nine images for each subject were averaged.

**Chemicals.** All chemicals were obtained from Sigma Chemical.

**Data analysis.** Data from multiple rings from the same subject were averaged; n refers to the number of subjects studied. Relaxation was calculated as the fractional decrement in contractile response induced by the preconstrictor agent before and after the addition of a vasodilator. The ethnic difference in mean contractility after norepinephrine was calculated with Student’s t-test. In addition, we used mixed linear regression modeling to assess ethnic differences in serial responses to different concentrations of the vasoactive drugs, with ethnicity as a fixed categorical subject factor. Based on the prior assumption that the correlation of the variance between measurements near to each other in time would be higher than between those further apart, we chose an autoregressive covariance structure as the most likely candidate structure and examined two other candidate structures (diagonal and compound symmetry) using the Akaike’s information criterion and Schwarz’s Bayesian information criterion (22). Data in square brackets are 95% confidence intervals, and one-sided P values of 0.05 or
less were considered statistically significant unless otherwise specified. Statistical analyses were performed with SPSS statistical software package for Windows (version 15.0, SPSS, Chicago, IL).

RESULTS

A series of tests was performed in resistance-sized arteries obtained from 31 normotensive women (20 self-defined white women and 11 self-defined black women). Baseline characteristics of the participants are shown in Table 1. There were no significant differences in patient characteristics between groups. Omental biopsies were obtained within 30 min after delivery in all patients, and vessels were isolated within 2 h. Isolated vessels have a limited lifespan, and the effects of CK inhibitors are irreversible. Therefore, we tested the vessels in two series: the first series included 8 white and 5 black patients (maximum contractility, bradykinin, and passive and active diameter-tension relations) and the second series included 12 white and 6 black patients (DNFB, SNP, amlodipine, AK inhibitors, and t-NNA). The results of the vessel studies with inhibitors are irreversible. Therefore, we tested the vessels in all patients, and vessels were isolated within 2 h. Absolute and relative differences were expressed as estimated marginal mean residual arterial contractilities of black and white women.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>White Women</th>
<th>Black Women</th>
<th>Differences (P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Media thickness, μm</td>
<td>20.0 (3.2)</td>
<td>22.6 (3.7)</td>
<td>0.62</td>
</tr>
<tr>
<td>Smooth muscle content, %</td>
<td>57.7 (4.7)</td>
<td>55.3 (5.4)</td>
<td>0.75</td>
</tr>
<tr>
<td>Collagen content, %</td>
<td>42.3 (3.9)</td>
<td>44.7 (5.4)</td>
<td>0.83</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 4 white women and 3 black women. Smooth muscle and collagen content are presented as percentages of the vessel wall. P values are two-sided.

DISCUSSION

Our data indicate that the maximum contractility response of isolated resistance arteries to norepinephrine is higher in normotensive black women than in white women (Fig. 2). There were no differences in passive or active tension-diameter relationships or histology as assessed by electron microscopy. This implies that functional rather than structural differences contributed to the greater contractility responses in black women.

Black people have been reported to have greater vascular contractility in vivo, and this has been attributed to an imbalance between contractile and vasodilation responses (3, 5, 27). In the vascular wall, two major factors have been suggested to explain the enhanced contractility, high CK (5) and low NO (27), but data on resistance arteries are lacking. As CK is bound at contractile proteins near ATPases, where the enzyme rapidly regenerates ATP for vascular contractility (3, 5, 10, 14, 19, 36), the higher vascular contractility found in black people may be associated with high CK. There is mounting evidence that mean serum and tissue CK activity are higher in black people than in other ethnic groups studied (1, 2, 3–6, 8). Our group (5) has previously shown that CK is associated with blood pressure in the general population, with a 14-mmHg increase in systolic blood pressure per log CK increase. The highest CK activities and blood pressure levels were found in black people, but the association was independent of ethnicity (2, 5, 8).

In this study, there were two important findings with regard to CK. First, we showed, in isolated human resistance vessels, that CK inhibition with the specific CK inhibitor DNFB significantly reduced the main part of vascular contractile responses. Second, a higher DNFB concentration was needed to reduce the contractility in arteries of black women, which suggests that vascular CK concentration is higher. We found

Table 3. Electron microscopic characteristics of the resistance artery wall

<table>
<thead>
<tr>
<th>Parameter</th>
<th>White Women</th>
<th>Black Women</th>
<th>Differences (P Value)</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
</tbody>
</table>

Values are means ± SE; n = 4 white women and 3 black women. Smooth muscle and collagen content are presented as percentages of the vessel wall. P values are two-sided.

Table 2. Ethnic differences in the contractility characteristics of isolated resistance-sized arteries

<table>
<thead>
<tr>
<th>Contractile Response</th>
<th>White Women</th>
<th>Black Women</th>
<th>Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum contractility, mN</td>
<td>8.9 ± 1.4</td>
<td>14.0 ± 1.8</td>
<td>5.1</td>
</tr>
<tr>
<td>Residual contractility, %</td>
<td>27</td>
<td>96</td>
<td>0.001</td>
</tr>
<tr>
<td>Dinitrofluobenzene</td>
<td>28 ± 4</td>
<td>55 ± 6</td>
<td>27</td>
</tr>
<tr>
<td>Sodium nitroprusside</td>
<td>75 ± 10</td>
<td>76 ± 12</td>
<td>1</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>75 ± 8</td>
<td>82 ± 14</td>
<td>7</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>78 ± 6</td>
<td>98 ± 7</td>
<td>19</td>
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Residual contractility values were expressed as estimated marginal means of residual contractility after the use of increasing concentrations of vasodilating agents. Absolute and relative differences were expressed as estimated marginal mean residual arterial contractilities of black and white women.

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no evidence of a significant contribution of AK to vascular contractility.

High CK might enhance contractility through greater ATP-buffering capacity at myosin ATPase but also lower NO bioavailability, because of a greater creatine demand with high CK (21). Creatine and NO are both synthesized from the semiessential amino acid l-arginine, but creatine synthesis, which occurs in the kidney and the liver, demands nearly 10 times the flux of plasma l-arginine represented by NO synthesis (37). Therefore, high creatine synthesis may decrease the availability of l-arginine and the rate of NO synthesis (Fig. 1) (5). Despite intracellular l-arginine concentrations that should saturate endothelial NOS, the rate of NO synthesis is limited by the rate of endothelial l-arginine uptake (5, 37).

NO is thought to be involved in the adaptive changes of the cardiovascular system during normal pregnancy, including decreased peripheral resistance, decreased mean blood pressure, and increased in uteroplacental blood flow (26, 27). Decreased bioavailable NO is considered to be a main causal factor in preeclamptic pregnancies (17, 27), and l-arginine has been shown to have beneficial effects on preeclampsia in some studies (15, 27, 33). In this study, we found evidence of reduced NO synthesis in normotensive pregnant black women but not in white women, in the reduced vasodilation response to bradykinin and the lack of vasoconstriction after the competitive NOS inhibitor L-NNA. Responses to NO donation through SNP were similar in both ethnic groups, suggesting that the cGMP-mediated pathways are intact in black women. Also, in line with clinical findings (7), we found no ethnic differences in the effect of Ca^{2+} blockers on vasodilation of isolated arteries.

The main strength of our study is that we assessed biological parameters of pressor responses in isolated resistance arteries from normotensive pregnant black and white women. To our knowledge, this is the first study on ethnic differences in resistance artery contractility in pregnant women. In our in vitro setting, we were able to study the resistance artery proper, without risk to the mother or child, and to precisely measure the contractile force of these small arteries (quantified in mN). This study yielded information on the understudied structural and functional characteristics of human resistance vessels during pregnancy, including maximum contractility responses as a primary outcome, as well as hypothesis-generating data on CK- and NO-dependent responses. The estimation of CK with DNFB has been validated (38). The immediate fall in tension in resistance arteries with the use of DNFB is similar to that reported in skeletal muscle of CK knockout mice, pointing to a direct inhibiting effect of DNFB on CK (31). Because of the small size of the vessels, microvascular CK activity could not be assessed directly with the gold standard of spectrophotometric enzyme assays. As a measure of vascular CK activity, we quantified CK spectrophotometrically in larger (renal) arteries and found evidence of higher CK activity in normotensive blacks than in whites (4). A limitation of our study is that the small sample size, due to the limited access to vessels, as the cesarean birth rate in healthy normotensive women is actively kept low in The Netherlands, the limited arterial lifespan ex vivo, and the use of irreversible drugs in the tests. However, the sample size was calculated to be sufficient for the primary and other main outcomes, and the ethnic differences in maximum contractility and responses to DNFB were quite apparent.

In summary, reducing racial disparities in pregnancy-related health and mortality is a major public health goal that can be achieved only by understanding the multiple causes (18, 35). Environmental and biological factors are thought to act in concert to cause more severe hypertension and a steeper rise in pregnancy-related hypertension in black people of all socioeconomic backgrounds (9, 16, 18, 35), with up to five times higher maternal death rates in black women (23). In search for new risk factors for these disparities, we found that the maximum contractile force in isolated resistance arteries from normotensive pregnant black women is greater than in vessels from white women. We detected no ethnic differences in the structure of the microvessels. We did find evidence of greater activity of the CK ATP-buffering system, which rapidly replenishes ATP at contractile proteins, and of lower microvascular NO synthesis. We conclude that the microvascular characteristics of black pregnant women may contribute to the greater risk for pregnancy-related hypertensive disorders in this population subgroup. Our observations in normotensives may imply that the black population is at risk for a further incline in hypertensive disorders during pregnancy.

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

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