Identification of a region of rat chromosome 1 that impairs the myogenic response and autoregulation of cerebral blood flow in fawn-hooded hypertensive rats

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Pabbidi MR, Juncos J, Juncos L, Renic M, Tullos HJ, Lazar J, Jacob HJ, Harder DR, Roman RJ. Identification of a region of rat chromosome 1 that impairs the myogenic response and autoregulation of cerebral blood flow in fawn-hooded hypertensive rats. Am J Physiol Heart Circ Physiol 304: H311–H317, 2013. First published November 9, 2012; doi:10.1152/ajpheart.00622.2012.—This study examined the effects of transfer of a 2.4-Mbp region of rat chromosome 1 (RNO1) from Brown Norway (BN) into fawn-hooded hypertensive (FHH) rats on autoregulation (AR) of cerebral blood flow (CBF) and the myogenic response of middle cerebral arteries (MCAs). AR of CBF was poor in FHH and FHH1BN congenic strains that excluded the critical 2.4-Mbp region. In contrast, AR was restored in FHH1BN AR+ congenic strains that included this region. The diameter of MCAs of FHH rats increased from 140 ± 14 to 157 ± 18 μm when transmural pressure was increased from 40 to 140 mmHg, but it decreased from 137 ± 5 to 94 ± 7 μm in FHH1BN AR+ congenic strains. Transient occlusion of MCAs reduced CBF by 80% in all strains. However, the hyperemic response following ischemia was significantly greater in FHH and AR− rats than that seen in AR+ congenic strains (AR−, 173 ± 11% vs. AR+, 124 ± 5%). Infarct size and edema formation were also significantly greater in an AR− strain (38.6 ± 2.6 and 12.1 ± 2%) than in AR+ congenic strains (27.6 ± 1.8 and 6.5 ± 0.9%). These results indicate that there is a gene in the 2.4-Mbp region of RNO1 that alters the development of myogenic tone in cerebral arteries. Transfer of this region from BN to FHH rats restores AR of CBF and vascular reactivity and reduces cerebral injury after transient occlusion and reperfusion of the MCA.

cerebral blood flow; middle cerebral artery; autoregulation of CBF; t-MCAO; ischemic stroke

AUTOREGULATION (AR) of cerebral blood flow (CBF) is a vital homeostatic mechanism that maintains constant oxygen delivery to the brain despite fluctuations in cerebral perfusion pressure (3, 6, 7, 22). AR protects the brain from increases in capillary hydrostatic pressure, vascular damage, and edema following elevations in arterial pressure and from ischemic injury following blockage of cerebral arteries or reductions in mean arterial pressure (MAP) (7). The myogenic response in the cerebral circulation is impaired following ischemic and hemorrhagic stroke and traumatic brain injury, and it is shifted to higher pressures in hypertension (6, 22, 24). There is also evidence that impairments in AR of CBF may contribute to the development of vascular dementia and Alzheimer’s disease (4, 24). Despite the importance of the myogenic AR of CBF, the mechanisms involved are not fully understood. Even less is known about genetic determinants of myogenic response. Part of the reason has been the lack of an animal model exhibiting impaired myogenic response in the cerebral circulation.

The fawn-hooded hypertensive (FHH) rat is a genetic model of hypertension (23) that is very susceptible to renal end-organ damage (11). We reported that the myogenic response of renal interlobular arteries and AR of renal blood flow (RBF) is impaired in FHH rats compared with fawn-hooded low-pressure rats (29, 30). More recently, we found that the substitution of a 99.4-Mbp region of rat chromosome 1 (RNO1) from Brown Norway (BN) to FHH rats between markers D1Rat183 and D1Rat76, along with a 12.9-Mb region in the q-terminus of RNO1, restored AR of RBF and reduced proteinuria in a FHH1BN dual congenic strain (31). Subsequently, we developed a congenic substrain that narrowed the region of interest to a smaller 4.7-Mbp region on RNO1 (strain B, Fig. 1). However, no studies were performed to determine whether the myogenic response of the renal afferent arteriole is altered in FHH rats or whether the myogenic response is restored in FHH1BN congenic strains. Moreover, no studies have examined whether the impaired myogenic response in FHH rats is specific to the renal circulation or reflects a more general vascular defect. Indeed, a recent report suggested that the myogenic response of mesenteric arteries is not altered in FHH rats (20).

Thus the present study examined the hypothesis that FHH rats have a mutation in a gene in the previously described region on RNO1 (31) that impairs the myogenic response in cerebral arteries and AR of CBF. This hypothesis was tested by comparing AR of CBF, the myogenic response of isolated middle cerebral arteries (MCAs) and cerebral ischemia-reperfusion (I/R) injury in FHH rats and in FHH1BN congenic strains in which a 2.4-Mbp region of RNO1 from 258.8 to 261.2 Mbp was transferred from BN rats into the FHH rat genetic background.

METHODS

General. Experiments were performed on 118 9–12-wk-old male FHH and FHH1BN congenic rats that were obtained from inbred colonies maintained at the University of Mississippi Medical Center (UMMC) and Medical College of Wisconsin (MCW). All the rats were housed in the Animal Care Facilities at the UMMC and MCW, which are both approved by the American Association for the Accreditation of Laboratory Animal Care. The rats had free access to food and water throughout the study. All protocols received approval...
Intramedic Fisher Scientific, Pittsburg, PA) was placed into the trachea, and the animals were mechanical ventilated throughout the experiment to maintain PO2 and PCO2 at 100 and 35 Torr, respectively. The rats were anesthetized with ketamine (30 mg/kg im, Phoenix Pharmaceutical, Sigma, St. Louis, MO) and NaCl. After being weaned, the pups were switched to a purified AIN-76 rodent diet containing 0.4% NaCl (Dyets, Bethlehem, PA). Colonies were maintained on a rodent diet purchased from LabDiet (PMI Nutrition International, Brentwood, MO) containing 0.28% NaCl. After being weaned, the pups were switched to a purified AIN-76 rodent diet containing 0.4% NaCl (Dyets, Bethlehem, PA).

**Protocol 1: AR of CBF in FHH and FHH.1^BN congenic strains.** These experiments were performed on 9–12-wk-old male FHH rats that were placed in the supine position. A polyethylene cannula (PE-240, Intramedic Fisher Scientific) was placed in the femoral artery for the measurement of arterial pressure and femoral vein for an intravenous infusion of 0.9% NaCl solution at a rate of 100 μl/min to replace surgical fluid losses. The rats were placed on a heating pad to maintain temperature at 37°C.

After the head of the rat was secured in a stereotaxic apparatus (Stoelting, Wood Dale, IL), the scalp was removed over the parietal cranial bone. A 3 x 3 mm area of the left and right parietal bones, 2 mm distal to bregma and 7 to 8 mm from center line, was thinned with a handheld low-speed drill until superficial pial vessels became visible. The windows were made slowly and often cooled with saline. CBF was monitored bilaterally with a laser-Doppler flow meter (Perimed, PF5001, Jarfalla, Sweden) and 1-mm flow probes. The probes were lowered into position using micromanipulators, and a drop of mineral oil was applied to the probe tip to provide optical coupling. After surgery and a 30-min equilibration period, MAP was adjusted to 90–100 mmHg by deepening the depth of anesthesia using a low dose of pentobarbital sodium (1–5 mg/kg iv). Baseline regional cerebral blood flow was measured and phenylephrine was infused intravenously. Phenylephrine was then sequentially lowered in steps of 10 to 40 mmHg by the withdrawal of the infusion. MAP was allowed to return to control by withdrawing phenylephrine infusion. MAP was then sequentially lowered in steps of 10 to 40 mmHg by the withdrawal of small amounts of venous blood. MAP was allowed to stabilize for 5 min at each level of MAP to ensure buildup of metabolic mediators, after which rCBF was recorded. rCBF was expressed as a percentage of baseline laser-Doppler flow signal.

The CBF autoregulatory index (AI) was calculated as the percent change in CBF/percent change in MAP. According to this analysis, an index of arterial pressure and cerebral blood flow was measured and phenylephrine was infused intravenously. Phenylephrine was then sequentially lowered in steps of 10 to 40 mmHg by the withdrawal of the infusion. MAP was allowed to return to control by withdrawing phenylephrine infusion. MAP was then sequentially lowered in steps of 10 to 40 mmHg by the withdrawal of small amounts of venous blood. MAP was allowed to stabilize for 5 min at each level of MAP to ensure buildup of metabolic mediators, after which rCBF was recorded. rCBF was expressed as a percentage of baseline laser-Doppler flow signal. The CBF autoregulatory index (AI) was calculated as the percent change in CBF/percent change in MAP. According to this analysis, an index of cerebral ischemia-reperfusion (I/R) injury. Rf-1 and -2, renal failure 1 and 2 regions, respectively (2, 14); CBF, cerebral blood flow; Add3, adducin 3; DUSP5, dual-specificity phosphatase 5; ND, not determined.

**Fig. 1.** Genetic map of the introgressed region in FHH.1^BN congenic strains. Genomic segments from the fawn-colored hypertensive (FHH) and Brown Norway (BN) rat are presented as white and black bars, respectively. Top: formal designations of congenic strains A–E based on the recommended “Guidelines for Nomenclature of Mouse and Rat Strains” presented on the Rat Genome Database (RGD@ncw.edu). Left: some of the polymorphic genetic markers used to genotype these strains. Right: 16 genes that map to the 2.4-Mbp region of interest on rat chromosome 1 according to the Rat Genome Database (RGD, RGSC Genome Assembly v3.4). Bottom: summary of our phenotype data for FHH rats and the various FHH.1^BN congenic strains. Plus (+) and minus (−) refer to the presence and absence of autoregulation (AR) of CBF, the myogenic response in isolated middle cerebral arteries, and a larger or normal infant size follow cerebral ischemia-reperfusion (I/R) injury. Rf-1 and -2, renal failure 1 and 2 regions, respectively (2, 14); CBF, cerebral blood flow; Add3, adducin 3; DUSP5, dual-specificity phosphatase 5; ND, not determined.
of 0 indicates perfect AR of CBF, whereas an index of 1 is characteristic of a circulation with a fixed vascular resistance.

Protocol 2: myogenic response in isolated MCAs. The rats were anesthetized with 4% isoflurane, and the brain was removed and placed in ice-cold physiological salt solution containing (in mM) 119 NaCl, 4.7 KCl, 1.17 MgSO₄, 1.6 CaCl₂, 12 NaHCO₃, 1.18 NaH₂PO₄, 0.03 EDTA, and 10 glucose (pH 7.4). MCAs were removed and mounted on glass pipettes and pressurized to 40 mmHg. The cannulated vessels were visualized using a videomicroscopy system (model KP130; Hitachi, Denshi, Tokyo, Japan), and a stereomicroscope (model DRC; Zeiss, Oberkochen, Germany). Vascular diameter was measured using a videomicrometer (VIA-100, Boeckeler Instruments, Tucson, AZ). After a 30-min equilibration period, a control myogenic response curve was constructed by measuring internal diameter of the vessels in response to increases in transmural pressure from 40 to 140 mmHg in steps of 20 mmHg. After a control relationship was determined, the bath was replaced with Ca²⁺-free physiological salt solution and the measurements repeated.

Protocol 3: transient MCA occlusion. Anesthesia was induced with 4% isoflurane and maintained with 1.5% isoflurane using a gas mixture of 30% oxygen and 70% nitrogen through an inhalation mask. Body temperature was continuously monitored and maintained at 37°C. Catheters were placed in the femoral artery and vein for the measurement of MAP and the infusion of drugs. The skull was exposed, and the bone was thinned bilaterally, 6 mm lateral and 2 mm posterior to bregma, for measurement of cCBF using laser-Doppler flowmetry. Focal cerebral ischemia was induced using the intraluminal suture method as previously described (19, 21). Briefly, the right common, internal and external carotid arteries were exposed through a midline incision of the neck. An 18-mm segment of nylon suture (4-0; Ethicon) coated at the tip with silicon (Xantopren VL plus; Heraeus Kulzer Dental Products Division, South Bend, IN) was introduced from the bifurcation into right internal carotid artery after ligation of the right common and external carotid arteries. The suture was advanced to the origin of the MCA and the internal carotid artery until cCBF fell by 80%. After 60 min of MCA occlusion (MCAO), the suture was removed to allow reperfusion. cCBF and MAP were continuously recorded for a 60 min ischemic period, followed by 120 min of reperfusion. The femoral catheters were removed, and the animal was allowed to recover from anesthesia. After 24 h of reperfusion, the rats were reanesthetized with 4% isoflurane and euthanized by decapitation. The brains were removed, cut into six 2-mm-thick coronal sections, and stained with 2% 2,3,5-triphenyltetrazolium chloride at 37°C for 30 min to measure infarct volume. After being washed, the slices were fixed with 10% buffered formalin solution. Cortical and subcortical infarct volumes were measured using MetaMorph digital imaging software. Infarct volume was expressed as a percentage of the area of the ischemic hemisphere.

Statistical analysis. Data are presented as mean values ± SE. The significance of differences in mean values was determined using a paired t-test (2 samples) or an analysis of variance for repeated measures, followed by a Holm-Sidak test. A P < 0.05 was considered to be significant.

RESULTS

Protocol 1: AR of CBF in FHH and FHH.1BN congenic strains. A genetic map comparing the regions of BN RNO1 introgressed into the various FHH.1BN congenic strains are presented in Fig. 1. We previously reported that transfer of a 99-Mbp region of rat RNO1 from BN rats from markers D1Rat183 to D1Rat76 along with a 4.7-Mbp region on q-term of RNO1 restored AR of RBF in a FHH.1BN dual congenic strain B (31). However, it remains to be determined whether the genes in the region specifically alter the myogenic response in the kidney or alter vascular function in general. Thus, in the present study, we compared AR of CBF and the myogenic response in cerebral arteries in FHH rats and this dual congenic strain B. We also studied AR of CBF in a FHH.1BN AR⁺ control strain A that is identical to strain B in the 99-Mbp region of RNO1 but excludes the 4.7-Mbp region of interest between genetic markers D1Rat376 and D1Rat225. In addition, we created and studied two additional dual congenic strains C and D that split the 4.7-Mbp region of interest. FHH.1BN congenic strain C has a 2.3-Mbp region of BN RNO1 introgressed between genetic markers D1Rat376 and D1Rat90, whereas strain D has a 2.4-Mbp region of BN RNO1 introgressed between markers D1Rat90 and D1Rat225 in a genetic background identical to the dual FHH.1BN congenic strain B. Afterward, we found that AR of CBF was restored in the dual congenic strain D and we backcrossed them with FHH rats and intercrossed the progeny to create a new minimal FHH.1BN congenic strain E in which the 99-Mbp region of BN RNO1 in congenic strains A through D reverted back to FHH alleles, whereas the 2.4-Mbp region of BN RNO1, spanning markers D1Rat90 to D1Rat225, was retained. The rat genome database (http://rgd.mcw.edu) currently reports that there are

Fig. 2. Autoregulation of CBF in 12-wk-old FHH rats and FHH.1BN congenic strains. A: relationship between CBF measured by laser-Doppler flowmetry and mean arterial pressure (MAP). B: autoregulatory indexes (AIs) calculated for an elevation in MAP from 100 to 150 mmHg. Mean values ± SE are presented. Numbers in parentheses indicate number of animals studied per strain. *Significant difference from the control value at 100 mmHg within a strain; †significant difference from the corresponding value in FHH rats.
16 known and predicted genes in this region (Fig. 1). Of these genes, only 3 [adducin-γ (Add3), dual-specificity phosphatase 5 (DUSP5), and X-prolylaminopeptidase 1] have any known influence on cardiovascular function.

A comparison of AR of CBF in FHH and the FHH.1BN congenic strains A–E are presented in Fig. 2. CBF increased by 40% in response to an elevation in MAP from 100 to 150 mmHg in FHH rats. Similar results were obtained in AR–FHH.1BN congenic strains A and C in which regions of BN RNO1 other than the 2.4-Mbp region of interest between markers D1Rat09 and D1Rat225 were introgressed. AR of CBF was markedly improved in the AR+ dual congenic strains B and D in which regions spanning the 2.4-Mbp region of BN RNO1 was introgressed. Similarly, AR of CBF was also improved in the minimal FHH.1BN congenic strain E. A summary of the AR observed in FHH rats and the congenic strains are presented in Fig. 2B. The CBF ARs averaged ~0.8 in FHH rats and AR– congenic strains A and C. The CBF ARs were significantly lower in AR+ FHH.1BN congenic strains B, D, and E.

A comparison of the CBF autoregulatory responses of FHH rats and the congenic strains to reductions in MAP produced by graded hemorrhage are presented in Fig. 3. CBF decreased by about 40% as MAP was reduced by 50% from 80 to 40 mmHg (Fig. 3A). CBF AIs averaged 0.8 in FHH rats and the FHH.1BN congenic strains. In contrast, CBF was better preserved and fell to a lesser extent (about 25%) in the AR+ FHH.1BN congenic strains B, D, and E in response to the same stimulus.

Protocol 2: comparison of myogenic response in isolated MCAs of FHH rats and FHH.1BN congenic strains. A comparison of myogenic response of MCAs of FHH rats and FHH.1BN congenic strains is presented in Fig. 4A. The myogenic response of MCAs isolated from FHH rats was impaired, and the diameter of these vessels increased significantly from 140 ± 14 to 157 ± 18 μm when transmural pressure was increased from 40 to 140 mmHg. The MCAs isolated from the AR− FHH.1BN congenic strain A also exhibited a minimal myogenic response, and diameter only fell from 144 ± 17 to 129 ± 23 μm in response to the same elevation in transmural pressure. In contrast, the diameter of MCAs isolated from FHH.1BN congenic strains B, D, and E decreased by 35, 40, and 35%, respectively, when transmural pressure was elevated from 40 to 140 mmHg (Fig. 4A). We did not study the myogenic response in MCAs obtained from line C because this region was excluded from consideration as they failed to exhibit AR of CBF. After calcium was removed from the bath, the pressure diameter relationship of MCAs isolated from FHH rats was unchanged, indicating that these vessels fail to develop any myogenic tone. In contrast, the diameter of vessels isolated from congenic strains B, D, and E increased, and these vessels dilated in response to elevations in transmural pressure. However, to simplify the figure, only the data from FHH rats and representative data from the FHH.1BN congenic strain E are presented in Fig. 4B.

Protocol 3: comparison of CBF, infarct size, and edema formation in FHH and FHH.1BN congenic strains after transient MCAO. Experiments were also performed to determine whether the impaired myogenic response of MCAs in FHH rats...
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Fig. 5. Changes in regional CBF measured by laser-Doppler flowmetry in response to transient occlusion and reperfusion of the middle cerebral artery in FHH rats and FHH.1BN congenic strains. Mean values ± SE are presented. Numbers in parentheses indicate number of animals studied per strain. *Significant difference from the corresponding value in FHH rats.

![Chart showing changes in regional CBF](chart)

Fig. 6. Infarct size (A) and edema formation (B) following 1 h of transient middle cerebral artery occlusion and 24 h of reperfusion in FHH and FHH.1BN congenic strains. A and B: representative images of the size of the infarct typically following transient middle cerebral artery occlusion in FHH rats and the minimal congenic strain in which autoregulation was restored. Infarct size is presented in A as a percentage of total hemispheric size, and edema is presented in B as a percentage of the increase in area of the ischemic hemisphere relative to the contralateral control side. Mean values ± SE are presented. Numbers in parentheses indicate number of animals studied per strain. *Significant difference from the corresponding value in line A.

![Chart showing infarct size and edema formation](chart)
Since FHH rats are reported to be a hypertensive strain, one might consider that the differences in the myogenic response of the MCAs of FHH rats and the congenic strain might be secondary to differences in blood pressure between the strains. However, the term fawn-hooded hypertensive strain is a bit of a misnomer since we have reported that they only exhibit a small 10-mmHg increase in blood pressure relative to other strains between 18 and 21 wk of age (14, 31). Blood pressure measured by telemetry was not significantly different in 9–12-wk-old FHH rats and congenic strains A and B (31). More recently, we have also compared blood pressure measured by telemetry in FHH rats and all of the congenic strains used in the present study. We found that blood pressure was not significantly different in any of the strains between 9 and 15 wk of age and averaged ~120 mmHg (R. J. Roman and M. Burke, unpublished observations). Thus it is unlikely that the phenotypic changes we have observed in the myogenic response of cerebral arteries and AR of CBF is secondary to structural or adaptive changes in the cerebral vasculature.

The present study also examined the CBF responses in FHH and the congenic strains to reductions in MAP caused by graded hemorrhage. The results in the FHH rats and congenic strain A were very consistent with the lack of AR to elevations in pressure in these strains and indicated that there was a ~40% fall in CBF in response to a 50% reduction in MAP. This suggests that FHH rats have very little ability to compensate to reductions in MAP by dilating the cerebral circulation. In contrast, CBF fell significantly less in the congenic strains B, D, and E in which the myogenic response was restored. These findings suggest that there is likely some degree of resting myogenic tone in the cerebral circulation in these congenic strains that could be withdrawn in response to a fall in MAP from 80 to 40 mmHg. The lack of compensation to reductions in MAP seen in the FHH and the FHH.1BN congenic strain A was a bit surprising since the release of metabolic vasodilators such as acetylcholine, ATP, adenosine, epoxyeicosatrienoic acids, and nitric oxide are thought to contribute to this response. The lack of response implies that whatever the genetic defect that impairs the myogenic response in cerebral arteries, it must also affect the ability of these vessels to dilate to these metabolic mediators as well.

One would also predict that the lack of AR in the brain of FHH rats should make them more vulnerable to the effects of I/R injury. The restoration of myogenic response and AR of CBF in the AR+ FHH.1BN congenic strains suggests that they should be more able to prevent the transmission of elevated systemic pressure to the brain following elevations in MAP and opposes the development of cerebral edema and injury. In support of this later conclusion, we found that FHH rats and the AR− FHH.1BN congenic strain A exhibited a exaggerated and prolonged hyperemia following t-MCAO relative to FHH.1BN congenic strains B and D in which AR was restored. Moreover, infarct size and edema of the brain was significantly greater in the congenic strain that did not autoregulate CBF than in those in which AR was restored. These results are consistent with the view that activation of the myogenic response contributes to the rapid normalization of CBF following cerebral I/R. This limits the rise in capillary pressure and swelling of the brain which then influences cerebrospinal fluid pressure and ultimately blood flow and infarct volume in the ischemic penumbra.

The myogenic response is an intrinsic property of the vascular smooth muscle cell that involves calcium influx via voltage gated calcium channels that leads to vasoconstriction (3). Increase in intracellular Ca2+ activates large-conductance K+ channels that hyperpolarize the membrane and oppose the myogenic response (8). The genes in the region of interest on RNO1 between D1Rat09 and D1Rat225, which impair myogenic response in FHH rats, remains to be determined. The region of interest on RNO1 in minimal congenic FHH.1BN strain E in which CBF AR was fully restored contains only 16 genes. Examination of the genes in the region indicates that there are two genes, DUSP5 and Add3, that may have some impact on vascular function. DUSP5 is a member of the DUSP gene family that dephosphorylates critical signaling molecules such as MAPK, ERK, and JNK that are involved in pressure- or stretch-induced myogenic responses (15, 18, 25). The other gene of interest is the Add3 gene, which was one of the first genes reported to cosegregate with the development of hypertension in a cross of Milan normotensive and Milan hypertensive rats (32). Subsequently, evidence has emerged linking mutations in adducin isoforms to the development of hypertension and other forms of cardiovascular disease in rats and humans (1, 5, 13, 26–28). Add3 promotes the spectrin-actin binding and controls the rate of actin polymerization by capping actin filaments at the plasma membrane (16, 17). Add3 is also a calmodulin binding protein and serves as a substrate for protein kinase C and Rho kinase (9, 10), both of which are important regulators of vascular tone. Furthermore, the administration of a pseudosubstrate inhibitor for protein kinase C has been shown to prevent the myogenic response in cerebral arterioles (12).

Perspectives. The results of the present study suggest that the lack of AR of CBF in FHH rats is due to impaired myogenic response in cerebral arteries, and there is a gene(s) that lies in the 2.4-Mbp region of RNO1 transferred from BN rats that restores the AR of CBF in FHH.1BN minimal congenic strain. The impaired myogenic response may enhance the transmission of systemic pressure to the cerebral microcirculation that promotes cerebral I/R injury in FHH rats. These results may provide information critical to the identification of new genes and therapeutic targets for the treatment of neurological damage associated with impaired AR CBF in hypertensive and diabetic patients and following stroke or traumatic brain injury and/or the cognitive decline associated with vascular dysfunction in aging.

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AUTHOR CONTRIBUTIONS

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