Modifications of Arterial Phenotype in Response to Amine Oxidase Inhibition by Semicarbazide

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Abstract—Semicarbazide-sensitive amine oxidase (SSAO)–deficient mice present no alteration in elastin cross-linking processes and carotid mechanical properties. In contrast, previous studies have shown that SSAO inhibitors induced marked anomalies in arterial structure and function. The aim of the present study was to examine the effect of semicarbazide (SCZ), an efficient SSAO inhibitor, on the arterial phenotype of the carotid artery in relation to modulation of SSAO and lysyl oxidase activities in growing rats. We first show that after 6 weeks of SCZ treatment (100 mg/kg per day), SSAO activity was reduced by 90%, whereas lysyl oxidase activity was only partially inhibited (<60%) in carotid artery, compared with controls. There was significant growth inhibition and no difference in mean arterial pressure but an increase in pulse pressure with a smaller arterial diameter in SCZ-treated rats. SCZ decreased aortic insoluble elastin without a change in total collagen. In addition, extracellular proteins other than insoluble elastin and collagen were increased in SCZ-treated rats. All of the elastic lamellae presented globular masses along their periphery, and focal disorganization was observed in the ascending aorta. Carotid artery mechanical strength was lower in SCZ-treated rats, and the elastic modulus–wall stress curve was shifted leftward compared with controls, indicating increased stiffness. Thus, SCZ modifies arterial geometry and mechanical properties, alters elastic fiber structure, and reduces the content of cross-linked elastin. Because these abnormalities are essentially absent in SSAO-deficient mice, our results suggest that lysyl oxidase inhibition is responsible for the major part of the vascular phenotype of SCZ-treated rats. (Hypertension. 2007;50:234-241.)

Key Words: SSAO ■ carotid artery ■ LOX ■ arterial stiffness ■ elastin

The maturation of elastin and collagen is crucial for the organization of the extracellular matrix (ECM) and to provide functional elasticity and tensile strength of the arterial wall. It is generally considered that the formation of intramolecular and extramolecular cross-links of both elastin and collagen is mediated by lysyl oxidase (LOX). LOX is a carbonyl-dependent copper enzyme, expressed, synthesized, and secreted by vascular smooth muscle cells.1 Many years ago, Lalich2 showed that the pharmacological inhibition of LOX with β-aminopropionitrile (BAPN) induced aortic ruptures and aneurysms in rat. Mice lacking LOX do not deposit normal elastic fibers and develop aortic aneurysms.3,4

Another copper-containing amine oxidase, semicarbazide-sensitive amine oxidase (SSAO), also called vascular adhesion protein-1, is highly expressed in the plasma membrane of vascular smooth muscle cells of the aortic media.5–7 The exact roles of SSAO in vascular wall function remain unknown. Several previous results support the hypothesis that SSAO may be involved in vascular smooth muscle cell differentiation, organization of the ECM,8 and regulation of vascular tone.9–12 Langford et al11 have shown that pharmacological inhibition of SSAO induced by semicarbazide (SCZ) in a growing rat model led to striking elastic fiber disorganization, possibly because of reduced cross-linking of elastin monomers. SCZ is the reference compound for inhibiting SSAO activity, but it was shown long ago to be able to inhibit collagen cross-linking, an effect that was attributed to LOX inhibition.13,14 Alternatively, it has been suggested that SSAO could influence arterial vascular tone, although contradictory results have been reported.9,15,16 Vidrio et al9 have proposed that SSAO-mediated hydrogen peroxide production could increase vascular tone and enhance hydralazine-
induced vasodilation. Interestingly, Conklin et al.\textsuperscript{16} have suggested recently that, in isolated human arteries, SSAO activation by methylamine mediated a vasorelaxant action. At a molecular level, it is conceivable, in view of previous results using molecular modeling,\textsuperscript{17} that, in addition to soluble primary amines, such as methylamine or aminoacetonitrile, SSAO may act on amino acids included in matrix proteins and, thus, contribute to physiological cross-linking of elastic and collagen fibers. Indeed, a recent study\textsuperscript{8} has demonstrated that SSAO-catalyzed deamination of methylamine results in formaldehyde–protein cross-linkage. In contrast with these observations, we have very recently demonstrated that SSAO-deficient mice present no alteration in the organization of the elastic fiber network, elastin cross-linking, and vascular endothelial or smooth muscle function,\textsuperscript{18} a result that does not support a major role of SSAO in these processes, and vascular endothelial or smooth muscle function.\textsuperscript{18} a result that does not support a major role of SSAO in the rodent arterial wall, even if unknown compensatory mechanisms can contribute to the phenotype in this model. However, the only detectable alteration in SSAO-deficient mice was an increase in carotid diameter, in line with a potential involvement of SSAO in arterial growth and/or the pathophysiology of aneurysms, as suggested previously.\textsuperscript{11,19}

Therefore, the objective of this study was to investigate in detail the specificity of SCZ treatment in growing rats on the vascular phenotype using different and complementary techniques: in vivo evaluation of diameter and elasticity of carotid arteries (CAs), in vitro determination of mechanical strength, and the study of the organization, morphology, and biochemical properties of elastic fibers.

Methods

Animals and Treatment

The study was performed in 21-day-old male Sprague–Dawley rats (Ifa-Credo). After weaning, animals were treated daily by IP injection of either physiological saline (control, \(n=20\)) or 100 mg/kg injection of either physiological saline (control, \(n=20\)) or 100 mg/kg of SCZ (i.e., \(n=20\)) for 6 weeks. Then, animals were divided in 2 groups.

In the first group (7 control and 7 SCZ-treated rats), arterial diameter and blood pressure (AP) in the right CA of anesthetized rats were recorded simultaneously. The left CA was used for histomorphometric studies. The second group was composed of 13 control and 12 SCZ-treated rats. The right CA, which is free of collaterals, was carefully dissected and used for mechanical strength determination in vitro. The left CA was removed for SSAO and LOX activity measurements or histological studies. Elastin and collagen quantification were performed on the descending thoracic aorta. All of the procedures were in accordance with institutional guidelines for animal experimentation.

Enzyme Assays and Biochemical Determinations

SSAO enzyme activity was assayed on carotid homogenates using a fluorometric method as described previously.\textsuperscript{18} Carotid extracts were prepared and then tested for LOX activity as mentioned.\textsuperscript{20} Results are expressed in nanomoles of H\textsubscript{2}O\textsubscript{2} per hour per milligram of protein. Insoluble elastin, total collagen, and cell protein contents are measured on whole thoracic aortas using the method described previously.\textsuperscript{21}

In Vivo Mechanical Properties

We simultaneously recorded intra-arterial diameter (left CA) and blood pressure (right CA) in pentobarbital-anesthetized rat using an ultrasonic echo-tracking device (NIUS-01, Asulab SA) as described previously.\textsuperscript{22} The pressure measurement was made by using a catheter (0.5 cm of phycoerythrin-10 fused to 3 cm of phycoerythrin-50) connected to a Statham pressure transducer (P23 Db) and a Gould pressure processor. The relation between the pressure and the lumen cross-sectional area was fitted using an arc tangent function. Carotid cross-sectional distensibility, a derivative of this function, was used to assess the global elastic behavior of the artery. Circumferential wall stress and incremental elastic modulus (\(E_{inc}\)), which characterizes the intrinsic mechanical properties of the wall material, were calculated with the above-mentioned parameters and media cross-sectional area. The mechanical strength of the intact CA was characterized by determining the in vitro intraluminal pressure required to induce vascular wall rupture as described previously.\textsuperscript{23}

Histomorphometry, SSAO Immunostaining, and Confocal Microscopy

We determined the structure of CA and the aortic arch. The CA (\(n=11\) for each group) was fixed in 10% buffered formalin at each animal’s mean arterial pressure to provide conditions of fixation close to the physiological in situ state of the vessel. Aortic arches were removed from thoracic aortas sampled for biochemical determination (\(n=6\) for control and \(n=5\) for SCZ-treated group). All of the arterial samples were embedded in paraffin, and 6-μm sections were stained with orcein to demonstrate elastic fibers. Arterial thickness and media cross-sectional area were determined by computer-directed color analysis (QuanT Image software). Elastin and SSAO immunostaining were examined by confocal microscopy (Nikon PCM 2000) on 10-μm-thick freeze-dried, paraffin-embedded sections of ascending thoracic aortas or CAs (\(n=5\) in each group).

Statistical Analysis

All of the values are expressed as mean±SEM. Unpaired Student’s \(t\) tests were performed to compare control rats with SCZ-treated rats. Differences were considered significant at values of \(P<0.05\). To compare diameter and distensibility within the same pressure range in control and SCZ groups, we calculated the area under each diameter–pressure curve and each distensibility–pressure curve for the pulse pressure range common to both groups. To compare \(E_{inc}\) stress curves in controls and SCZ rats, we calculated the area between the \(E_{inc}\) axis and \(E_{inc}/\text{wall stress}\) curve within the range of \(E_{inc}\) common to both groups. Mean shifts of diameter, distensibility, and wall stress were used to compare control rats with SCZ-treated rats.

Results

SSAO and LOX Enzyme Activities in CAs of Control and SCZ-Treated Rats

To evaluate the efficiency of amine oxidase inhibition by SCZ, SSAO activity was first measured in CAs of control and SCZ-treated rats. After SCZ treatment and compared with that of control animals, SSAO activity in CAs was reduced by 90% (Table 1). We also tested whether SCZ in our experimental conditions had an effect on LOX activity. LOX activity was significantly decreased by 56% in CAs in SCZ-treated rats. Taken together, enzyme measurements in CAs indicated that both amine oxidase activities were inhibited by SCZ, with a 10-fold reduction for SSAO enzyme activity and a little more than a 2-fold reduction for LOX activity.

General and Hemodynamic Parameters

The body weight of SCZ-treated rats was significantly lower than that of control animals, and this was largely because of a marked lack of adipose tissue development, because various fat depots were reduced by 45% to 70% (data not shown). Nose–rump length was also reduced but to a much lesser extent. There was no change in heart rate or in the mean,
systolic, or diastolic arterial pressures. However, pulse pressure was slightly but significantly elevated in SCZ-treated rats (Table 1).

### In Vivo Mechanical Properties and Morphological Analysis of CA

Figure 1 shows diameter–AP, distensibility–AP, and Einc–wall stress in control and SCZ-treated rats. Table 2 indicates the mean values of mechanical and structural parameters of the CA. Within the common range of AP, the diameter–AP curve in the SCZ-treated group was significantly shifted downward from that of the control group (146-µm mean shift) indicating a smaller diameter for a given level of AP. Arterial diameter at mean arterial pressure was smaller in SCZ than in the control group (P<0.05), but this difference disappeared after adjustment for body weight (P=0.78). The distensibility–AP curves and distensibility at mean arterial pressure in the SCZ group were not significantly different compared with the control group. By contrast, the Einc–stress curve of SCZ rats was significantly shifted leftward (84-kPa mean shift), which indicated an increased stiffness of the wall material. There was no difference in Einc and wall stress calculated at mean arterial pressure. Media thickness was significantly higher in SCZ-treated than in control rats. Media cross-sectional area was not significantly higher in SCZ (P=0.33) -exposed animals, but the difference became significant after adjustment for body weight (P<0.05).

The in vitro rupture pressure was significantly lower in SCZ-treated compared with control rats (Figure 2A), indicating a reduction in the mechanical strength of the arterial wall after chronic SCZ exposure. The rupture of the vascular wall was confirmed by histological examination of en face preparations. Complete wall rupture occurred perpendicular to the long axis of the arterial segment (Figure 2D and 2E), and in SCZ-treated rats, the number of wall ruptures was 3 times higher than in control rats (Figure 2B). The total area occupied by these ruptures was significantly higher in SCZ than in control rats (Figure 2C), confirming an increased wall fragility.

### Morphology of CA and Aorta

The morphology of formalin-fixed, paraffin-embedded control and SCZ-treated CAs is shown in Figure 3. In SCZ-treated rats, CAs appeared to have a smaller diameter, a thicker wall, and more undulating elastic lamellae (Figure 3A and 3B). The mean number of elastic lamellae did not differ between control and SCZ-treated rats, but interlamellar spaces generally appeared wider in the latter than in control rats (Figure 3C and 3D). Apart from this, there was no obvious anomaly in the structure and the organization of the elastic lamellae in the CA at low magnification (Figure 3C and 3D), but at high magnification, all of the elastic lamellae presented globular masses of orcein-stained material along their periphery and in the interlamellar space (Figure 3F). In control rats, such deposits were not seen, the periphery of the fibers presenting more of the aspect of small fibrils (Figure 3E). Similar alterations were observed in aortas (Figure 3G and 3H), in which ECM components have been measured.

SSAO distribution and alterations of elastic fibers were examined in CAs by confocal microscopy (Figure 4A through 4C). SSAO immunostaining (red) was mainly associated with elastic lamellae (green-yellow) but was also present in the

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![Figure 1](https://example.com/figure1.png)

**Figure 1.** Mean CA diameter–AP curves (A), cross-sectional distensibility–AP curves (B), and Einc–wall stress curves (C) in control (n=7) and SCZ-treated rats (n=7). The diameter–AP curve of the SCZ-treated group was significantly shifted downward vs controls. No difference in arterial distensibility was observed between the 2 groups. The Einc–stress curve of SCZ-treated rats was significantly shifted to the left vs controls. Values are mean±SEM; *P<0.05; SCZ-treated rats vs control rats.
interlamellar spaces. The density and distribution of SSAO did not differ between groups. Interlamellar spaces were wider in all of the SCZ-treated rats. In rare cases, SCZ induced severe alterations of carotid elastic lamellae, which appeared to end in a frayed, sparse hairy aspect (Figure 4B). Elastic fibers of similar aspect were also observed in the interlamellar space (Figure 4C). These were never observed in control rats.

The effects of SCZ were more pronounced in the aorta than in the CA. In the aorta, the number of elastic lamellar interruptions was higher in SCZ-treated rats (Figure 4E) than in control rats (Figure 4D). Focal areas of elastic lamellar disorganization and disappearance were observed in 3 of 5 SCZ-treated rats (Figure 4F). These alterations were absent in control rats.

**Quantification of Aortic Insoluble Elastin and Total Collagen**

Results are summarized in Figure 5. The dry weight (milligrams per centimeter) of the thoracic aorta was significantly higher in the SCZ-treated group than in the control group. Although this difference was small (~9%), it was even more significant when considering the lower body weight and smaller size of the treated group. This increase was attributed largely to an increase in the quantity of ECM, because cell protein content did not differ significantly between the 2 groups (controls: 0.525±0.04 mg/cm; SCZ: 0.552±0.004 mg/cm; P not significant). Insoluble elastin, expressed both as a percentage dry weight or as milligrams per centimeter, was markedly reduced in the treated group, whereas total collagen was either unchanged (percentage of dry weight) or slightly increased (milligrams per centimeter). Thus, our results suggest that, in the treated group, there is a significant decrease in cross-linked elastin and an increase in ECM proteins other than insoluble elastin and collagen.

**TABLE 2. In Vivo Vascular Mechanical Parameters in Control and SCZ-Treated Rat CAs**

<table>
<thead>
<tr>
<th>Parameters at Mean Arterial Pressure</th>
<th>Control</th>
<th>SCZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumen diameter, mm</td>
<td>1.160±0.045</td>
<td>1.031±0.046*</td>
</tr>
<tr>
<td>Distensibility, 10⁻³ mm Hg⁻¹</td>
<td>6.6±1.4</td>
<td>5.3±0.7</td>
</tr>
<tr>
<td>Incremental elastic modulus, kPa</td>
<td>966±172</td>
<td>876±141</td>
</tr>
<tr>
<td>Wall stress, kPa</td>
<td>408±30</td>
<td>314±36</td>
</tr>
<tr>
<td>Medial thickness, μm</td>
<td>40±1</td>
<td>49±2†</td>
</tr>
<tr>
<td>MCSA, mm²</td>
<td>0.086±0.004</td>
<td>0.094±0.006</td>
</tr>
</tbody>
</table>

Values are mean±SEM of 7 control and 7 SCZ-treated rats. MCSA indicates media cross-sectional area.
*P<0.05; †P<0.001 SCZ-treated vs control animals.

Figure 2. Mechanical strength and wall ruptures of the CAs in control (n=13) and SCZ-treated rats (n=12). The rupture pressure was significantly lower in SCZ-treated rats vs control rats (A). In SCZ-treated rats, the number of the ruptures (B) and the total area occupied by ruptures (C) were significantly higher than in control rats. En face preparations of CA showing wall ruptures perpendicular to the long axis of the arterial segment (objective magnification, ×10). Values are mean±SEM; *P<0.05; ***P<0.005: SCZ-treated vs control animals.
Our results show that SCZ administered over the period of rapid growth produced both an almost complete blockade of vascular SSAO activity, associated with a strong inhibition of LOX. Overall, SCZ caused a reduction in vessel diameter and insoluble elastin content and an increase in ECM components other than collagen and insoluble elastin. In parallel, SCZ-treated rats showed a decreased pressure of rupture of the CA and an increased arterial stiffness.

In the study by Langford et al., chronic exposure to SCZ was reported to induce marked reduction in SSAO activity with no significant decrease in LOX activity, associated with marked alterations in arterial wall structure and a decrease in insoluble elastin. Nevertheless, these authors reported that MDL-72274 or MDL-72145, characterized as specific SSAO inhibitors, were able to induce a significant reduction in aortic LOX activity. In our in vivo experiments, we show that LOX activity was inhibited by \( >50\% \) in CAs, whereas that of SSAO was almost complete. It, thus, appears that no highly specific inhibitor of SSAO activity exists. In addition, we have shown recently that mice lacking SSAO were characterized by an absence of variations in mature elastin content and structural abnormalities of the vascular wall. It is, thus, very likely that LOX inhibition may be responsible for the decrease in insoluble elastin content observed here with SCZ treatment.

Several studies have suggested that SSAO may be involved in elastic fiber organization. It has been reported that, in transgenic mice overexpressing SSAO in vascular smooth muscle cells, an abnormal structure of the aortic elastic lamellae is observed. We have shown recently that in idiopathic annuloaortic ectasia disease, there was a dramatic downregulation in SSAO expression in the affected areas that was correlated with a reduction in elastic lamellar thickness.

Our results show that SCZ induced morphological alterations of elastic lamellae in the CA and a reduction in the amount of insoluble elastin, which corresponds with mature, cross-linked elastin. Soluble non–cross-linked elastin was not quantified. The nature of the ECM proteins other than insoluble elastin and collagen, which increased after SCZ treatment, is open to speculation. The most likely hypothesis is that they represent proteoglycans associated with tropoelastin. Indeed, proteoglycans have been shown previously to be increased when elastin (and collagen) cross-linking is inhibited by \( \beta \)-aminopropionitrile fumarate (BAPN).

Microscopic examination revealed more severe disorganization of elastic lamellae in the ascending thoracic aorta than in the CA. This is not surprising and is also the case when rats are treated with BAPN (M. Osborne-Pellegrin, unpublished observations, 1989). This may simply be the reflection of the magnitude of hemodynamic forces acting on the arterial wall or it may suggest that substances that affect cross-linking have the greatest effect in arteries where the ECM content is highest. The globular deposits on the periphery of the elastic fibers seen were not visible in confocal microscopy. This suggests that the antibodies used in confocal microscopy did not react with these globular structures, which probably represent non–cross-linked tropoelastin associated with proteoglycans, as has been well documented after BAPN administration.

Administration of SCZ decreased the rupture pressure of the carotid wall, indicating an increased vascular wall fragility at high levels of stress. Collagen cross-linking is generally considered to be responsible for mechanical strength of

**Figure 3.** Morphology of control and SCZ-treated rat arteries. Transverse sections of CAs and aortic arches were stained with orcein to show elastic fibers. Low (objective: \( \times4 \); A and B) and medium power (objective: \( \times40 \); C and D) views of CA showing general architecture of the elastic lamellae. High-power (objective: \( \times100 \); E and F) views of CA showing globular masses along the periphery of the elastic lamellae and in the interlamellar space. A similar structure of elastic lamellae is present in the aortic arch of SCZ-treated rats (objective: \( \times40 \); G and H; \( n=5 \) in each group).
tissues at high stress levels, but insoluble collagen was not measured here, and so we cannot directly evaluate collagen cross-linking. Our results suggest that elastin cross-linking was decreased, and so it is probable that collagen fibers were also affected. However, the small decrease in rupture pressure in SCZ-treated rats implied that residual cross-links were sufficient to limit the decrease in rupture pressure or that, alternatively, other cross-link–independent factors may be involved in providing mechanical resistance, such as adhesion proteins, and organization between these components.

One of the main results was the significant increase in arterial stiffness and pulse pressure in SCZ-treated rats. This represents one of the rare models in which increased pulse pressure is associated with qualitative modifications of arterial ECM, that is, reduced elastin cross-linking and an increase in some constituent other than collagen or insoluble elastin. Reduced cross-linking induced by BAPN administration has been reported previously to increase arterial elasticity.26–28 However, it may be conceived that, under certain conditions, a reduction in insoluble, mature elastin, the more distensible component of the vascular wall, may contribute, per se, to an increase in arterial stiffness. In addition, altered functional properties of elastin may transfer the mechanical load from elastin to collagen for lower circumferential stress in SCZ-treated rats, and, lastly, the significant increase in ECM proteins other than collagen or insoluble elastin could also contribute to enhance arterial stiffness. The decreased diameter in the SCZ-treated rats may be related to the marked reduction in body weight, because this difference was not significant after adjustment for body weight. Alternatively, it may be related to matrix hypertrophic remodeling toward an increase in ECM proteins and in arterial stiffness that for equivalent levels of circumferential wall stress reduces the distension of the artery. We should emphasize that the increase in arterial dry weight occurred despite the overall growth-inhibitory effect of SCZ. The latter appeared essentially related to reduction in white adipose tissue.

Mechanical, morphological, and biochemical studies clearly illustrate that striking differences exist between the vascular phenotype of SCZ-treated rats and that of SSAO

Figure 4. Confocal microscope images of the CA in control and SCZ-treated rats. Immunostaining of elastin (green) and SSAO (red) in CAs from a control rat (A), and SCZ-treated rats (B and C) showing widened interlamellar spaces, branching of elastic lamellae, and a sparse hairy aspect of some elastic fibers in SCZ-treated rats (arrows). D through F, thoracic aorta from a control rat (D), and SCZ-treated rat (E and F) showing focal interruptions (arrow), disorganization, and disappearance of elastic lamellae in SCZ-treated rats (n=5 in each group).
impedance were observed in mice lacking the descending aorta, an increase of thickness of the wall, attributable to SSAO inhibition. A decrease in diameter of the arteries observed in SCZ-exposed animals.18 Therefore, these effects of SCZ cannot be attributable to SSAO inhibition. A decrease in diameter of the descending aorta, an increase of thickness of the wall, fragmentation of elastic fibers, and an increase in aortic impedance were observed in mice lacking the Lox gene.4 Although the LOX−/− mice died very early after birth, these alterations of the vascular wall are compatible with arterial changes observed in SCZ-treated rats. Therefore, our results suggest that inhibition of LOX is most likely responsible for the major part of the vascular phenotype of SCZ-treated rats, in agreement with the 56% reduction in LOX activity.

Perspectives

In our study, it must be underlined that pharmacological inhibition of SSAO and LOX using SCZ should be interpreted relative to the phase of arterial maturation, whereas the mouse models of LOX and SSAO invalidation should be interpreted in the context of early arterial development. Although the major part of the SCZ-induced vascular phenotype is likely to be related to LOX inhibition, we cannot exclude that some vascular effects of SCZ on the vascular wall are mediated by SSAO inhibition, such as the increase in ECM proteins other than collagen and insoluble elastin, associated with arterial mechanical properties not observed with BAPN.26–28 Our observations provide further insight into the effects of SCZ in vivo, which is an important issue, because some authors have suggested that the SCZ-induced vascular phenotype is mainly mediated by SSAO inhibition.10,11 Further studies will be required to determine the respective age-dependent involvement of LOX and SSAO in vascular physiology. Several studies have shown that high plasma SSAO activity is observed in arterial diseases.29 It would be of great interest to investigate mechanisms by which these amine oxidases could affect vascular wall structure and function. Because SSAO activity is much higher in the human than in the rodent arterial wall,30–32 defining the exact implication of SSAO in physiology and pathology of human arteries remains a major challenge.

Sources of Funding

This work was supported by funding from Inserm, the Agence Nationale de la Recherche, and the Region Lorraine.

Disclosures

None.

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_Hypertension._ 2007;50:234-241; originally published online April 23, 2007; doi: 10.1161/HYPERTENSIONAHA.107.089292

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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