Effect of Treatment on Flow-Dependent Vasodilation of the Brachial Artery in Essential Hypertension

Maria Lorenza Muiesan, Massimo Salvetti, Cristina Monteduro, Damiano Rizzoni, Roberto Zulli, Claudia Corbellini, Claudia Brun, Enrico Agabiti-Rosei

Abstract—The aim of our study was to evaluate the effect of antihypertensive treatment on flow-mediated dilation (FMD) of a large artery, a noninvasive estimate of endothelial function, in hypertensive patients. In 78 consecutive hypertensive patients (40% men; age range, 42 to 67 years) we measured by a high-resolution ultrasound system the changes of brachial artery diameter during reactive hyperemia and after sublingual glycyl trinitrate (400 μg); brachial artery flow velocity was measured by pulsed Doppler. The results of 2 studies are reported. In the first study, this procedure was repeated in 58 patients after 6 and 12 months of treatment with a combination of antihypertensive drugs; in a second study, the FMD was assessed in 20 patients after 2 months of monotherapy with either nifedipine or hydrochlorothiazide. In the first study, FMD was significantly increased after treatment compared with baseline (from 3.1 ± 3% at baseline to 6.5 ± 4.5% at 6 months and to 8.12 ± 4.6% at 12 months; P < 0.001 by ANOVA), concomitant with blood pressure reduction (from 162 ± 24/102 ± 13 mm Hg to 141 ± 12/89 ± 6 mm Hg and to 141 ± 9/89 ± 6 mm Hg; P < 0.001 by ANOVA); significant changes of endothelium-independent dilation were also observed, but only after 12 months of treatment (from 14.2 ± 4.8 at baseline to 15.5 ± 4.7 at 6 months and 16.8 ± 5.9% at 12 months; P = 0.03 by ANOVA). In the second study, FMD was significantly increased during nifedipine treatment as compared with baseline (from 5 ± 6.18% at baseline to 9.45 ± 3.94%, P < 0.001), while it did not change in patients receiving hydrochlorothiazide (from 5.15 ± 5.28% at baseline to 4.69 ± 4.34%, NS). No significant changes of endothelium–independent dilation were observed with both drugs (from 17.10 ± 2.4% to 18.14 ± 3.76% and from 18.73 ± 4.07% to 17.46 ± 4.27% during nifedipine and hydrochlorothiazide, respectively, NS). Thus, in essential hypertensive patients an improvement of the impaired FMD of the brachial artery, evaluated by noninvasive ultrasound, may be observed after long-term, effective blood pressure reduction, suggesting a beneficial effect of antihypertensive treatment on endothelial function. It seems that beyond blood pressure control, a calcium antagonist may be more effective than a diuretic in this respect. 

(Hypertension. 1999;33[part II]:575-580.)

Key Words: vasodilation ■ arteries, brachial ■ hypertension, essential ■ antihypertensive therapy ■ blood pressure

Endothelial cells play an important regulatory role of the vascular tone and the structure in humans. 1,2 Nitric oxide, synthesized by the vascular endothelium, causes relaxation of vascular smooth muscle, 3,4 inhibition of platelet aggregation, 5 and cell proliferation 6 through the activation of soluble guanylate cyclase and the increase of intracellular cyclic guanosine monophosphate (GMPc) levels, which in turn lower intracellular calcium levels. A dysfunction of the vascular endothelium has been implicated in the pathophysiology of several cardiovascular diseases, including essential hypertension. Several studies have shown a blunted decrease in forearm blood flow induced by Nω-monomethyl-L-ester (L-NMMA) 7 or an impairment in the vasodilator response of different vascular beds to acetylcholine 8–11 in hypertensive patients compared with normotensive control subjects, while the response to sodium nitroprusside or other direct vasodilators was maintained. All these studies have used invasive procedures. A noninvasive method has been developed 12 for the measurement by ultrasound of the dilation of a large artery in response to an increase in flow and shear stress. The dilation of the vessel, obtained via release of nitric oxide, 13–17 is impaired when endothelial dysfunction is present. By means of this method an impairment of flow-mediated dilation (FMD) of the brachial artery has been shown in uncomplicated hypertensive patients 18,19 and in patients with several cardiovascular risk factors. 12,20 In addition, the brachial artery dilator response to reactive hyperemia has been used to investigate reversibility of endothelial dysfunction in hypercholesterolemic adults, in postmenopausal women, and in patients with heart failure 21–26 but not in hypertensive patients.

Received September 16, 1998; first decision October 12, 1998; revision accepted October 26, 1998.
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In experimental hypertension, endothelial dysfunction may be reversed by antihypertensive treatment, \(^{27-29}\) whereas in humans this goal seems to be more difficult to achieve. \(^{30,31}\) Interestingly, it has been suggested that some antihypertensive agents, such as ACE inhibitors \(^{32,33}\) and calcium antagonists, \(^{34,35}\) may be particularly effective in improving endothelial dysfunction. Therefore, the aim of this study was to evaluate the effect of antihypertensive treatment on changes of FMD in hypertensive patients.

**Methods**

Seventy-eight consecutive patients (48 men and 30 women; age range, 42 to 67 years) with newly diagnosed or poorly controlled essential hypertension were included in the study. They had a clinical blood pressure reading (the average of 3 different sphygmomanometric measurements, each performed on 3 separate days) of >140/90 mm Hg. The possibility of secondary causes of hypertension was excluded by standard clinical and laboratory tests. Subjects with severe hypercholesterolemia (>7.76 mmol/L), diabetes mellitus, aortic or cerebrovascular ischemic heart disease, impaired renal function, or other major diseases were excluded from the study. All women were in the postmenopausal state. Thirty-one patients had never been treated previously, and 47 stopped their previous medication (a diuretic or a \(\beta\)-blocker) at least 4 weeks before the study. Twenty patients were former smokers, and 18 patients were strongly advised to stop smoking. The current number of cigarettes and the duration of smoking were recorded. Blood was drawn on the day of the ultrasound procedure, after fasting and abstinence from smoking for 12 hours, and total serum cholesterol, triglyceride, and glucose levels were determined.

In all patients, a noninvasive 24-hour blood pressure monitoring (Spacelabs 90209, Spacelabs Inc) was performed at baseline and after treatment (after 12 months in the first study and after 2 months in the second study). Patients were fitted with the monitor on the morning of the day of blood sampling and ultrasound procedure. The interval between recordings was 20 minutes (for further details about the method, see reference 36).

High-resolution ultrasound was used to measure changes in brachial artery diameter, according to the previously described technique. \(^{15}\) Ultrasound studies were performed in the morning, after the patients had rested in a supine position for 30 minutes in a quiet room. It was possible to record good-quality scans using a 7.5-MHz linear array ultrasound probe (HP Sonos 1500 ECG unit, Hewlett Packard) by a single dedicated physician. Scans of the brachial artery approximately 5 cm above the elbow were obtained in longitudinal section, and the transducer was maintained in a fixed position relative to the patient’s arm. Arterial flow velocity was measured by means of a pulsed Doppler signal, with the sample volume placed in the center of the artery. Flow increase was induced using a blood pressure cuff placed around the arm and inflated to up to 300 mm Hg; after 5 minutes of arterial occlusion, the cuff was deflated. An interval of 20 minutes was allowed for vessel recovery, and sublingual glyceryl trinitrate (GTN spray; 400 \(\mu\)g) was administered. Scans were recorded twice at baseline, from 30 seconds before to 120 seconds after the release of occlusion (including a flow velocity recording 15 seconds after cuff release) and from 2 to 4 minutes after the administration of sublingual glyceryl trinitrate.

Vessel diameter was measured at end diastole from super-VHS recordings by 2 observers unaware of the patients’ clinical characteristics and treatments. Measurements were taken from the anterior to the posterior interface between the media and adventitia. For the reactive hyperemia scans, diameter measurements were taken from 30 to 90 seconds after cuff deflation, and the greatest diameter was used; 4 cardiac cycles were averaged for resting scans, reactive hyperemia, and glyceryl trinitrate administration. FMD and glyceryl trinitrate–induced dilation were determined as the percent diameter change relative to baseline measurements. Brachial blood flow was calculated from Doppler flow-velocity measurements. Repeated scans were recorded randomly and measured on 2 different occasions in a group of 20 patients. Interobserver and intraobserver coefficient of variation for measurements of FMD were 4% and 3.5%, respectively.

The protocol of the study was approved by the ethics committee of our institution (Medical School, University of Brescia), and informed consent was obtained from each participant. The procedures followed were in accordance with institutional guidelines.

In 58 patients randomized to multicenter ongoing or recently completed double-blind studies, the FMD was assessed in baseline conditions and after 6 and 12 months of antihypertensive treatment, including an ACE inhibitor or a dihydropyridine calcium antagonist or a \(\beta\)-blocker, in combination with a \(\beta\)-blocker.

Twenty patients (70% men; age range, 42 to 65 years; 10% smokers) were included in the second study, aimed to compare the effect of nifedipine and hydrochlorothiazide on FMD after 2 and 6 months of monotherapy; results obtained after 2 months of therapy are reported.

**Statistical Analysis**

Data were stored and analyzed with BMDP Statistical software programs 2V, LR, and 2R (BMDP Statistical Software Inc). All data are expressed as mean±SD. Differences between 2 means were compared with use of the paired or unpaired Student’s \(t\) test, with Bonferroni correction for multiple comparisons. The changes of FMD were analyzed by 1-way ANOVA and ANCOVA for repeated measures, including LDL cholesterol as covariate. The relationships between continuous variables were evaluated by linear regression. Differences were considered statistically significant at a level of \(P<0.05\).

**Results**

**First Study**

Basal demographic, hemodynamic, and humoral characteristics for the patients are summarized in Table 1. During treatment, a significant reduction of clinic blood pressure (at both 6 and 12 months) and 24-hour monitored blood pressure (at 12 months) was observed (Table 1). No changes in smoking habits in the 16 patients who smoked (3.2±4.9 pack/y) were observed during the treatment period.

Resting brachial artery diameter and blood flow did not differ in the whole group during treatment compared with baseline conditions (Table 1), whereas a trend toward a decrease in total and LDL cholesterol levels was observed.

A significant increase of FMD was observed after 6 months of treatment and improved further at 12 months of therapy (from 3.1±3% at baseline to 6.5±4.5% at 6 months and to 8.12±4.6% at 12 months; \(P<0.001\) by ANOVA) (Figure 1). After adjustment for LDL cholesterol modifications, changes of FMD remained significant (from 3.21±3.01% at baseline to 6.51±4.4% at 6 months and to 8.05±4.5% at 12 months; \(P<0.001\) by ANCOVA) The dilation induced by glyceryl trinitrate increased gradually in respect to that observed under basal conditions, and a significant change was observed only after 12 months (Figure 2; from 14.2±4.8% at baseline to 15.5±4.7% after 6 months and to 16.8±5.9% after 12 months; \(P=0.03\) by ANOVA). Since an increase in the hyperemic response, although not statistically significant, was observed at 6 and 12 months of treatment, the dilation/hyperemia ratio was calculated, and this ratio showed that the increase in flow was not related to the increase in the hyperemic response (FMD/hyperemic response increased from 0.008±0.11 at baseline to...
TABLE 1. Hemodynamic Characteristics of Patients Randomized to Long-Term Antihypertensive Treatment at Baseline and After 6 and 12 Months of Therapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline (n=58)</th>
<th>6 months (n=58)</th>
<th>12 months (n=58)</th>
<th>P (by ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical SAP/DAP, mm Hg</td>
<td>162±24/102±13 (125–250)/(80–150)</td>
<td>141±12/89±6 (119–164)/(79–101)</td>
<td>141±9/89±6 (120–164)/(76–101)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>24-h SAP/DAP, mm Hg</td>
<td>143±12/91±9 (117–168)/(74–110)</td>
<td>...</td>
<td>133±11/85±8 (115–157)/(64–106)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>6.33±0.90 (4.11–7.75)</td>
<td>6.23±0.93 (4.4–8.15)</td>
<td>6.13±1.01 (3.6–8.27)</td>
<td>.06</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>4.21±0.78 (2.53–5.12)</td>
<td>4.03±0.8 (2.53–5.69)</td>
<td>3.96±0.78 (1.94–5.3)</td>
<td>.06</td>
</tr>
<tr>
<td>Glycemia, mmol/L</td>
<td>5.33±0.6 (4.3–6.49)</td>
<td>5.38±0.6 (4.38–7.49)</td>
<td>5.49±0.66 (4.27–8.1)</td>
<td>.08</td>
</tr>
<tr>
<td>Brachial diameter, mm</td>
<td>4.3±0.77 (2.91–6.4)</td>
<td>4.2±0.7 (2.97–6.31)</td>
<td>4.21±0.7 (2.92–6.30)</td>
<td>.09</td>
</tr>
<tr>
<td>Baseline flow, mL/min</td>
<td>132±79 (27–411)</td>
<td>141±85 (38–406)</td>
<td>130±69 (40–306)</td>
<td>.4</td>
</tr>
<tr>
<td>Hyperemia, %</td>
<td>548±250</td>
<td>613±405</td>
<td>766±636</td>
<td>.3</td>
</tr>
</tbody>
</table>

Values are mean±SD, with range in parentheses. SAP/DAP indicates systolic arterial pressure/diastolic arterial pressure.

0.015±0.16 after 6 months and to 0.016±0.11 after 12 months; P<0.001 by ANOVA).

When individual changes were analyzed, an increase in the flow-mediated response to hyperemia >4%, which corresponds to the variation coefficient of the method, assessed in our laboratory was observed in 31 patients, while in 27 it remained unchanged.

Correlations between FMD and clinical or monitored systolic blood pressure values were not significant at baseline (r=−0.073 and r=0.16 for clinical and 24-hour systolic blood pressure, respectively), and a correlation of borderline significance was observed between FMD and systolic blood pressure after 12 months of treatment (r=−0.25, P<0.05, and r=0.17 for clinical and 24-hour systolic blood pressure, respectively). No correlation was observed between FMD and total or LDL cholesterol determinations at baseline (r=−0.06 and r=0.16 for total and LDL cholesterol, respectively) or during treatment (at 12 months: r=−0.17 and r=−0.02 for total and LDL cholesterol, respectively).

Second Study

The 2 groups of hypertensive patients, randomized to either nifedipine or hydrochlorothiazide, were not different in age, sex, clinical blood pressure, or total or LDL cholesterol levels (Table 2). Only 1 patient in the nifedipine and 1 in the hydrochlorothiazide group were smokers (10 versus 6.57 pack/y, respectively), and they did not change smoking habits. Clinical and monitored blood pressure values were reduced after 2 months of treatment in both groups (Table 2). Humoral parameters as well as resting brachial artery diameter and blood flow changes during treatment did not differ in the two groups of patients as compared with baseline conditions.

FMD was significantly increased during nifedipine treatment compared with baseline (from 5±6.18% to 9.45±3.94%, P<0.001), while it did not change in patients who received hydrochlorothiazide (from 5.15±5.28 at baseline to 4.69±4.34%; NS). After 2 months of treatment, no significant changes of endothelium-independent dilation were observed with either drug (from 17.10±2.4 to 18.14±3.76 and from 18.73±4.07 to 17.46±4.27% during nifedipine and hydrochlorothiazide treatments, respectively).

Discussion

The results of our study suggest that an improvement of endothelial dysfunction, as evaluated by noninvasive ultrasound assessment of the brachial artery dilation in response to reactive hyperemia, may be obtained by antihypertensive treatment.

Recent evidence proves the pivotal role of nitric oxide during reactive hyperemia, suggesting that the flow-dependent dilation of a large artery is mediated by nitric oxide. The noninvasive ultrasound method has been extensively used for the assessment of endothelial dysfunction of large, superficial systemic arteries in patients with several cardiovascular risk factors. In addition, a close correlation between endothelium-dependent vasoreactivity in...
TABLE 2. Hemodynamic Characteristics of Patients Randomized to Nifedipine Gastrointestinal Therapeutic System or Hydrochlorothiazide at Baseline and After 2 Months of Treatment

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Nifedipine (n=10)</th>
<th>HCTZ (n=10)</th>
<th>P (by ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>56±2</td>
<td>56±7</td>
<td>.9</td>
</tr>
<tr>
<td>Sex, F/M</td>
<td>3/7</td>
<td>3/7</td>
<td>NS</td>
</tr>
<tr>
<td>SAP/DAP, mm Hg</td>
<td>161±16/102±9</td>
<td>154±11/98±4</td>
<td>.22/.14</td>
</tr>
<tr>
<td>Brachial artery diameter, mm</td>
<td>4.35±0.54</td>
<td>4.32±0.55</td>
<td>.9</td>
</tr>
<tr>
<td>Flow-mediated dilation, %</td>
<td>5±6.18</td>
<td>5.15±5.28</td>
<td>.95</td>
</tr>
<tr>
<td>Baseline flow, mL/min</td>
<td>131±57</td>
<td>135±56</td>
<td>.86</td>
</tr>
<tr>
<td>Hyperemia (% increase in flow)</td>
<td>592±221</td>
<td>628±323</td>
<td>.92</td>
</tr>
</tbody>
</table>

After 2 months

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Nifedipine (n=10)</th>
<th>HCTZ (n=10)</th>
<th>P (by ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>145±10*/91±3*</td>
<td>136±10*/86±3*</td>
<td>.06/.4</td>
</tr>
<tr>
<td>Brachial artery diameter, mm</td>
<td>4.35±0.55</td>
<td>4.29±0.63</td>
<td>.84</td>
</tr>
<tr>
<td>Flow-mediated dilation, %</td>
<td>9.45±3.94*</td>
<td>4.69±4.34</td>
<td>.02</td>
</tr>
<tr>
<td>Baseline flow, mL/min</td>
<td>136±57</td>
<td>129±58</td>
<td>.5</td>
</tr>
<tr>
<td>Hyperemia (% increase in flow)</td>
<td>626±285</td>
<td>742±276</td>
<td>.78</td>
</tr>
</tbody>
</table>

Values are mean±SD. SAP/DAP indicates systolic arterial pressure/diastolic arterial pressure.

*P<0.01 versus baseline.

The brachial and coronary arteries has been reported, proving that endothelial dysfunction is a systemic process.21

The accuracy and reproducibility of this method has allowed the assessment of brachial artery endothelial dysfunction reversibility in patients with several cardiovascular risk factors or heart disease.22–26 In hypertensive patients, the impairment of endothelial function has been observed by this noninvasive technique in some18,19 but not in all studies.38,39 Laurent et al18 used a Doppler system for the measurement of brachial artery diameter, with a shorter period of ischemia of 2 minutes, that might have accounted for different results obtained. The influence of clinic blood pressure was examined by Celermajer et al39 in asymptomatic healthy subjects with different risk factors (but not hypertension); despite the fact that a linear inverse correlation between FMD and clinical systolic blood pressure was observed, systolic blood pressure did not enter in the multivariate relation as a major determinant.

We confirmed the impairment of endothelium-dependent dilation of the brachial artery in essential hypertensives. The lack of a correlation between the brachial artery flow-mediated dilation and 24-hour systolic blood pressure (in contrast to a previous study11 showing a correlation between the maximum acetylcholine-induced vasodilation and ambulatory monitoring blood pressure values) might be ascribed to the presence of several cardiovascular risk factors (such as smoking or hyperlipidemia) in our consecutive essential hypertensives.

Modulation of the endothelial function could represent an important therapeutic goal in the treatment of hypertensive patients, and this study has examined for the first time the changes during antihypertensive therapy of a large-artery response to reactive hyperemia.

In experimental hypertension, endothelial dysfunction may be reversed by antihypertensive treatment.27–29 although differences were observed among antihypertensive drugs (cilazapril and hydralazine) despite a similar reduction of blood pressure.28 In humans the improvement of endothelial dysfunction seems to be more difficult to achieve,30–33 and an additional beneficial effect, beyond blood pressure reduction, has been suggested for some antihypertensive agents. The beneficial effect of ACE inhibitors30,31 was related to the increased levels of bradykinin, while some calcium antagonists32,33 seem to possess antioxidant properties, with consequent enhanced nitric oxide bioavailability. Panza et al30 observed no improvement in the vascular response to acetylcholine and nitroprussate in hypertensive patients with normal blood pressure values who received long-term treatment with diuretics, β-blockers, verapamil, or ACE inhibitors in differing combinations. More recently, Schiffrin et al observed an improved relaxation to acetylcholine in small resistance arteries after 1 and 2 years of therapy with...
cilazapril\textsuperscript{12} as well as after 1 year of treatment with nifedipine in a slow-release formulation,\textsuperscript{38} while in both studies no change was observed in patients treated with atenolol, despite an equivalent hypotensive effect. The long-term treatment with lacidipine\textsuperscript{44} and lisinopril\textsuperscript{15} increased the response to acetylcholine infusion in the forearm circulation, although the mechanisms involved seem to be different.

In the first study, we examined patients participating in ongoing randomized studies and receiving treatment with ACE inhibitors, dihydropriydine calcium-antagonists, \(\beta\)-blockers, or diuretics; a limitation of the study is that we are not yet aware of the patients’ therapy, because of the double-blind studies design. In the first study, some patients showed no change of FMD (according to our laboratory reproducibility), despite a significant reduction of blood pressure. This suggests the possibility that shear-stress reduction, consequent to blood pressure decrease, may explain only in part the restoration of endothelial function; the preliminary results obtained in the second study, showing the lack of improvement of endothelial dysfunction in patients receiving a diuretic, seem to confirm this hypothesis.

We have also evaluated the changes of brachial artery diameter to glyceryl trinitrate, which produces vasodilation as a diuretic, seem to confirm this hypothesis. The vasodilator responses to glyceryl trinitrate increased slightly during long-term treatment, suggesting a regression of vascular structural changes. However, in addition to a possible reduction of vascular structural changes, a specific impairment of synthesis and/or release and/or biological activity of nitric oxide was confirmed when the diameter increase was corrected for the slight, and not statistically significant, increased postischemic flow response.

It is well known that dyslipidemia can affect endothelial function and that the concomitant presence of several risk factors further impairs endothelial-dependent relaxations.\textsuperscript{40,41} In our study, 31 patients had total cholesterol levels \(>6.46 \text{ mmol/L}\), and 39 patients had LDL cholesterol concentrations \(>4.14 \text{ mmol/L}\); however, no significant differences of FMD were observed at baseline when patients were subdivided according to these values (FMD = 2.82±2.9 versus 3.32±3.15 in patients with total cholesterol \(<6.46 \text{ mmol/L}\), and FMD = 2.95±3.16 versus 3.14±3.01 in patients with LDL cholesterol \(<4.14 \text{ mmol/L}\) versus \(>4.14 \text{ mmol/L}\), respectively). In addition, a slight and not significant reduction in serum total and LDL cholesterol concentrations was observed during long-term antihypertensive treatment in respect to baseline, and similar results were obtained when changes in FMD induced by long-term treatment were adjusted for plasma lipids levels. The evaluation of FMD in consecutive hypertensive patients with increased serum lipid concentrations, and not only in selected hypertensive patients free of other CV risk factors, seems to have clinical relevance. In fact, evidence from a recent multicenter European study\textsuperscript{42} has shown a considerable percentage of smokers and a slight elevation of total cholesterol levels (average total cholesterol, 5.82±0.98 mmol/dl; LDL cholesterol, 3.8±0.93 mmol/dl), similar to that observed in our population of consecutive hypertensive outpatients.

In conclusion, our data have shown that an improvement of the impaired FMD of the brachial artery, assessed by noninvasive ultrasound, may be observed after long-term, effective pharmacological blood pressure reduction, suggesting a beneficial effect of antihypertensive treatment on endothelial dysfunction. It seems that beyond blood pressure control, the treatment with the calcium antagonist nifedipine may be more effective in this respect.

References

Antihypertensive Treatment and Flow-Mediated Vasodilation


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Hypertension. 1999;33:575-580
doi: 10.1161/01.HYP.33.1.575
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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