Myocardial Perfusion During Long-Term Angiotensin-Converting Enzyme Inhibition or \( \beta \)-Blockade in Patients With Essential Hypertension

Niels H. Buus, Morten Bøttcher, Claus G. Jørgensen, Kent L. Christensen, Kristian Thygesen, Torsten T. Nielsen, Michael J. Mulvany

Abstract—Hypertension is associated with reduced coronary vasodilatory capacity, possibly caused by structural changes in the coronary resistance vessels. Because vasodilatory treatment may correct abnormal structure better than nonvasodilating treatment, we compared whether long-term angiotensin-converting enzyme (ACE) inhibition has a greater effect on coronary reserve and cardiovascular structure than \( \beta \)-blockade in patients with essential hypertension. Thirty previously untreated hypertensive patients were randomized in a double-blind design to treatment for 1 year with either perindopril (4 to 8 mg per day, \( n = 15 \)) or atenolol (50 to 100 mg per day, \( n = 15 \)) and furthermore compared with normotensive controls. Cardiac output and left ventricular mass were measured with echocardiography and resistance artery structure was determined in vitro. Using positron emission tomography, myocardial perfusion (MP) was determined at rest and during dipyridamole-induced hyperemia while still on medication. Perindopril reduced left ventricular mass by 14\% (\( P < 0.01 \)), peripheral vascular resistance by 12\% (\( P < 0.01 \)), and media thickness-to-lumen diameter ratio of resistance arteries by 16\% (\( P < 0.05 \)), whereas atenolol had no effect. Resting MP was decreased both by perindopril (−11\%, \( P < 0.01 \)) and by atenolol (−25\%, \( P < 0.01 \)) in parallel to the reduction in rate pressure product. Hyperemic MP was unaltered by perindopril (+2\%, \( P = \text{NS} \)), but reduced by atenolol (−32\%, \( P < 0.01 \)). Compared with atenolol, perindopril treatment resulted in higher coronary reserve (\( P < 0.05 \)). We conclude that compared with \( \beta \)-blockade, ACE inhibition increases coronary reserve and results in regression of hypertensive resistance artery structure and left ventricular hypertrophy. Vasodilating may thus be superior to nonvasodilating treatment in repairing the hypertensive myocardial microcirculation. (Hypertension. 2004;44:465-470.)

Key Words: hypertension, essential \( \ddagger \) arteries \( \ddagger \) myocardial \( \ddagger \) antihypertensive therapy \( \ddagger \) vascular resistance

Arterial hypertension is associated with alterations in myocardial hemodynamics such that coronary vasodilator capacity is reduced.1–4 This abnormality could result in reduced exercise capacity and myocardial ischemia in situations with high oxygen demands,1,4 but the background for this microcirculatory disturbance is not clear. The presence of left ventricular hypertrophy may contribute,6,7 but structural remodeling of myocardial resistance arteries also seems important.5

It is well established from hemodynamic measurements in the forearm8,9 and in vitro studies of isolated small arteries10,11 that the peripheral resistance vasculature is morphologically altered in essential hypertension. Whether myocardial and peripheral vascular morphology are affected similarly in hypertension remains to be confirmed, but coronary flow reserve has been negatively correlated with the media-to-lumen ratio of subcutaneous small arteries.12 This suggests that antihypertensive treatment that corrects the abnormal vascular structure could also correct the diminished coronary flow reserve. Previous studies have suggested that several antihypertensive treatments improve peripheral vascular structure,13 particularly those causing reduction in total peripheral resistance such as angiotensin-converting enzyme (ACE)-inhibitors.11,14,15 In contrast, nonvasodilating therapy with \( \beta \)-blockers leaves structure almost unchanged,11,14,16 The effect of antihypertensive treatment on myocardial perfusion (MP) has been investigated in a number of studies,2,4,17–20 ACE inhibitors4,19,20 have, with some exceptions,2 demonstrated reductions in myocardial vascular resistance, which is ascribed to structural repair of coronary arterioles.20

On this basis it might be expected that the reduced coronary reserve seen in hypertension would be improved by treatment with an ACE inhibitor, but not by a \( \beta \)-blocker. Improved coronary reserve has been observed previously with ACE inhibition,4,19,20 but the effect of prolonged \( \beta \)-blockade has been studied only to a limited extent.17 We have therefore made a direct comparison of the effect of ACE inhibitor and \( \beta \)-blocker treatment in patients with essential
hypertension. Because we were interested in the clinical consequences of the therapy, measurements were made during active medication rather than after drug washout. This also avoids the possible influence of increasing blood pressure (BP) and uncertain effects on vascular structure during washout.

Our hypothesis was that ACE inhibitor treatment would have a more beneficial effect on coronary reserve than β-blocker treatment. A subsidiary hypothesis was that any differences in the effect on coronary reserve would be associated with different effects on resistance artery structure. We therefore compared the effect of the 2 treatments on myocardial vascular resistance during hyperemia as well as on the structure of isolated subcutaneous small arteries.

Materials

Patients

Previously untreated patients were recruited from general practitioners and the outpatient clinic. Subjects could be included when sitting diastolic BP was 100 to 120 mm Hg, measured 3 times with a mercury sphygmomanometer, on 2 or 3 occasions during an observation period of 2 to 6 weeks. None of the patients had chest pain. Patients suspected of secondary hypertension underwent isotope renography (n=3), spiral computed tomographic scan of the renal arteries (n=2), or urinary sampling of catecholamines (n=1), but none showed signs of secondary hypertension, and all were included. Normotensive healthy controls were recruited through the local blood bank. The study was approved by the local ethics committee and participants signed an approved consent form before entering the study.

24-Hour BP Measurements

All participants had a 24-hour BP examination (SpaceLab ABP 90207). From 7 AM to 11 PM, BP and heart rate (HR) were measured automatically every 30 minutes and from 11 PM to 7 AM every 60 minutes. The patients all had average day time BP >135/85 mm Hg, whereas all controls had BP <130/80 mm Hg.

Treatment Protocol

After selection, the patients entered a placebo period of 3 to 4 weeks, during which posidon emission tomography (PET) scan, echocardiography, and subcutaneous biopsy were performed. After the placebo period, patients were randomly assigned to treatment with either perindopril or atenolol in a double-blind fashion. Dosage was adjusted to achieve a diastolic BP ≤90 mm Hg. Patients started with 1 daily capsule of either 4 mg perindopril or 50 mg atenolol. If diastolic BP was ≥90 mm Hg after 1 month, the dose was doubled to 8 mg perindopril or 100 mg atenolol. If necessary, 2.5 or 5 mg of bendroflumethiazide was added to achieve the target BP. After 1 year of treatment, and still on active medication, PET scan, echocardiography, and subcutaneous biopsy were repeated.

Left Ventricular Mass and Cardiac Output

Left ventricular (LV) mass and cardiac output were determined by echocardiography (Vingmed System 5; 1.7 MHz probe). LV diastolic diameter and posterior wall and septal thickness were assessed in M-mode images of the parasternal long-axis and short-axis view with 3 different measurements in each position. Furthermore, the left ventricular outflow tract diameter was measured and the stroke distance was determined as the area of the pulsed Doppler curve. The measurements were performed after 30 minutes of rest and BP was measured at the same time.

Resistance Artery Structure

Subcutaneous biopsy specimens were obtained from the gluteal area. Small arteries, with an estimated diameter of 100 to 300 μm, were dissected from the biopsy specimen and 2 artery segments were mounted as ring preparations in a myograph. Lumen diameter and media thickness were measured in a standardized way as previously described.

Measurement of MP

MP was quantified using PET (model EXACT HR 961; Siemens/CTI) with intravenous 13N-ammonia as perfusion tracer. A detailed description of the perfusion quantization has been previously published. MP was measured at rest and after intravenous infusion of dipyridamole (0.56 mg/kg) over 4 minutes. Image acquisition commenced 8 minutes after starting the dipyridamole infusion. BP and HR were measured immediately after each injection of 13N-ammonia using an automated sphygmomanometer. None of the participants had perfusion defects.

Calculations and Statistical Analysis

All data are given as mean±SEM. The rate pressure product (RPP) is defined as HR×systolic BP. Myocardial vascular resistance is defined as mean arterial BP (diastolic BP+1/3×pulse pressure) divided by MP. Coronary reserve is defined as hyperemic MP divided by resting MP. LV mass was calculated according to the formula. LV diastolic pressure (LVDP) was calculated as the outflow tract area×stroke distance×HR. Peripheric vascular resistance was determined as mean BP divided by cardiac output.

Primary effect parameters were MP and myocardial vascular resistance, whereas resistance artery media-to-lumen ratio, cardiac output, LV mass, and peripheric vascular resistance were secondary parameters. The effect of treatment in each group (perindopril or atenolol) was tested with a 2-tailed, paired Student t test on the changes in values seen in each patient. Differences in the effect of treatments on primary effect parameters were tested using analysis of covariance, with the treatment data as the fixed factor and baseline data as covariate. In case of rejection of normality, values were expressed as ranks and an ANCOVA analysis were performed. For the comparison of pretreatment data with the data from the control persons, the 2 treatment groups were pooled and differences were tested by a grouped t test. The post-treatment data were compared with controls using an unpaired t test. P<0.05 was considered significant.

Results

Demographic Data and Blood Pressure Reduction

Thirty-two patients were selected for the study. Two subjects were not included because of adverse reactions during the PET scan procedure. Table 1 shows baseline data for the 30 patients included and for the normotensive controls.

Full BP reduction (Figure 1) was achieved in the perindopril group with 4 mg (n=2), 8 mg (n=5), or 8 mg plus bendroflumethiazide (n=8), and in the atenolol group with 50 mg (n=9), 100 mg (n=1), or 100 mg plus bendroflumethiazide (n=5). After 1 year of treatment, ambulatory HR decreased significantly in the atenolol group (from 68±2 to 56±2 bpm, P<0.01), whereas no difference was seen in the perindopril group (from 77±1 to 76±1 bpm, P=NS).

Cardiac Output and Peripheral Vascular Resistance

Cardiac output was similar in patients and controls (2.75±0.06 versus 2.64±0.14 L/min per m², P=NS), whereas peripheral vascular resistance was increased in the patients (41.1±1.1 versus 34.5±1.7 mm Hg/L per min per m², P<0.01). In the perindopril group, cardiac output remained unchanged (+5±5%, P=NS), whereas it was re-
Peripheral vascular resistance was reduced by 12±6% in the perindopril group (P<0.01), whereas it remained unchanged in the atenolol group (−6±6%, P=NS). The 1-year treatment values in the perindopril group were not significantly different from control persons.

LV Mass
LV mass was on average 146±6 g/m² in the patients and 106±5 g/m² in controls (P<0.01). After 1 year, LV mass was reduced in the perindopril group by 14±4% (P<0.01), whereas no change was observed in the atenolol group (2±5%, P=NS). The 1-year treatment values were still higher in the perindopril group as compared with controls (P<0.05).

Resistance Artery Structure
Thirteen patients in the perindopril group, 14 patients in the atenolol group, and 14 controls underwent subcutaneous biopsy. Before treatment, media-to-lumen ratio was on average 8.05±0.35% in the patients and 5.89±0.28% in controls (P<0.01). After 1 year, media-to-lumen ratio was reduced by 15±4% (P<0.05) in the perindopril group but remained unchanged in the atenolol group (−5±6%, P=NS). The 1-year treatment values were still higher in the perindopril group as compared with controls (P<0.05).

Myocardial Perfusion and Vascular Resistance
Baseline BP, HR, and RPP at rest and during dipyridamole infusion were similar in the 2 treatment groups. After 1 year of treatment, BP was reduced in both groups. Both at baseline and during dipyridamole infusion, HR was markedly lower in the atenolol group (Table I, available online at http://www.hypertensionaha.org).

Resting MP was elevated in patients as compared with controls corresponding to the higher RPP (Table 2, Figure 2). During treatment, resting MP was significantly lowered in both groups but decreased more in the atenolol than in the perindopril group (Table 2, Figure 2). The reduction in RPP was 19±6% in the perindopril group and 37±2% in the atenolol group. However, resting MP correlated closely to the RPP before and after 1 year of treatment, the relation being similar for both treatments (Figure 3). The 1-year values of resting MP were not different from that of control persons in either of the treatment groups.

Hypertensives and controls showed no difference in dipyridamole-induced hyperemia, but patients had a reduced coronary reserve (Table 2, Figure 2). Perindopril and atenolol had remarkably different influence on dipyridamole-induced hyperemia, which was almost unaffected by perindopril but reduced by 32% by atenolol (Figure 2B and Table 2). The changes in resting and hyperemic perfusion resulted in an increased coronary reserve in the perindopril group as compared with the atenolol group (Table 2). In the perindopril-treated group, neither hyperemic MP nor coronary reserve was different from the values for control persons, whereas these parameters were still significantly reduced in atenolol-treated patients.

Resting myocardial vascular resistance was similar in patients and controls, and was slightly, but significantly, reduced by 3% during perindopril treatment and increased by 15% during atenolol treatment (Table 2). Hyperemic vascular resistance decreased by 8% in the perindopril group and markedly increased by 35% in the atenolol group (Table 2). There was a close linear correlation between resting and hyperemic vascular resistance before and after 1 year of treatment (Figure 4). Resting and hyperemic myocardial vascular resistance were, in the perindopril-treated group, reduced to the level of control persons.

Correlations
Changes in media-to-lumen ratio did not correlate to changes in either resting (r²=0.01, P=NS) or hyperemic MP (r²=0.01, P=NS). Changes in peripheral vascular resistance did not correlate to changes in either resting (r²=0.06, P=NS) or hyperemic myocardial vascular resistance (r²=0.01, P=NS).

| TABLE 1. Clinical Characteristics of Hypertensive Patients and Controls |
|-----------------|-----------------|-----------------|
| Perindopril | Atenolol | Controls |
| Males/females | 10/5 | 12/3 | 10/5 |
| Age, y | 49±2 | 51±2 | 49±1 |
| Body mass index, kg/m² | 27.1±0.5 | 26.6±0.6 | 25.1±0.6* |
| Smokers | 6 | 4 | 6 |
| 24-hour systolic pressure, mm Hg | 153±2 | 152±3 | 123±3† |
| 24-hour diastolic pressure, mm Hg | 100±2 | 101±2 | 79±2† |
| 24-hour heart rate, bpm | 81±2 | 75±3 | 74±2 |
| Total cholesterol, mmol/L | 5.5±0.2 | 5.5±0.2 | 5.6±0.2 |
| LDL cholesterol, mmol/L | 3.3±0.3 | 3.3±0.2 | 3.4±0.2 |
| HDL cholesterol, mmol/L | 1.7±0.1 | 1.5±0.1 | 1.6±0.1 |
| Triglycerides, mmol/L | 1.3±0.2 | 1.5±0.2 | 1.4±0.2 |
| Fasting glucose, mmol/L | 5.1±0.1 | 5.0±0.1 | 4.8±0.1 |

LDL indicates low-density lipoprotein; HDL, high-density lipoprotein.
*P<0.05, †P<0.01 controls vs pooled patient data.

Figure 1. Ambulatory blood pressure during run-in (~1 month), placebo (time=0), and active treatment (1 to 12 months).
The present study demonstrates different effects of vasodilating and nonvasodilating antihypertensive therapy on coronary reserve and cardiovascular structure. Thus, treatment with ACE inhibition increased coronary reserve compared with β-blockade measured during strong pharmacologically induced vasodilation with dipyridamole. This was associated with a marked increase in minimal myocardial vascular resistance with β-blockade, whereas this remained unchanged by ACE inhibition with corresponding findings regarding the structure of subcutaneous small arteries. Furthermore, during both treatments, there was a close relation between resting and hyperemic myocardial vascular resistance, suggesting that improvement in coronary reserve requires reduction in resting vascular resistance.

In a literature survey, we reported that reduction of peripheral minimal vascular resistance in hypertensive patients is obtained only in treatment regimens that reduce BP by lowering vascular resistance rather than by lowering cardiac output. Thus, ACE inhibitor-based treatments normally result in reductions in resting and minimal vascular resistance, associated with improvement of artery structure. However, β-blocker–based treatments do not affect either resting or minimal vascular resistance, and they leave artery structure unchanged. The resistance artery, cardiac output, and peripheral vascular resistance data obtained in the present study support these previous findings.

The effect of ACE inhibition to reduce LV mass is well-known, although the mechanisms remain partly unsolved. However, a reduction in peripheral vascular resistance, and thus LV afterload, may contribute. Although perindopril treatment was followed by reduced left ventricular hypertrophy and myocardial vascular resistance, the β-blocker–treated group experienced an increased myocardial vascular resistance despite a constant LV mass. This

### Table 2. Myocardial Perfusion and Vascular Resistance

<table>
<thead>
<tr>
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<th>Perindopril</th>
<th>Atenolol</th>
<th>Controls</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>1 Year</td>
<td>Difference</td>
</tr>
<tr>
<td><strong>Myocardial perfusion</strong></td>
<td></td>
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<tr>
<td>(mL/min per gram)</td>
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<td></td>
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<tr>
<td>Rest</td>
<td>0.95±0.04</td>
<td>0.84±0.05∗</td>
<td>−0.11±0.04</td>
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<tr>
<td>Hyperemia</td>
<td>2.27±0.18</td>
<td>2.15±0.11</td>
<td>−0.12±0.15</td>
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<tr>
<td>Coronary reserve</td>
<td>2.39±0.17</td>
<td>2.64±0.17</td>
<td>0.24±0.19</td>
</tr>
<tr>
<td>Hyperemia</td>
<td>122±5</td>
<td>117±6∗</td>
<td>−5±5</td>
</tr>
<tr>
<td><strong>Myocardial vascular resistance</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>(mm Hg/mL per min per gram)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>122±5</td>
<td>117±6∗</td>
<td>−5±5</td>
</tr>
<tr>
<td>Hyperemia</td>
<td>54±4</td>
<td>47±3∗</td>
<td>−7±3</td>
</tr>
</tbody>
</table>

∗P<0.01 compared to baseline value.
†P<0.05 compared to perindopril treatment.
‡P<0.01 compared to perindopril treatment.
§P<0.05 controls vs pooled patient data at baseline.
¶P<0.01 controls vs 1 year treatment.

**Discussion**

The present study demonstrates different effects of vasodilating and nonvasodilating antihypertensive therapy on coronary reserve and cardiovascular structure. Thus, treatment with ACE inhibition increased coronary reserve compared with β-blockade measured during strong pharmacologically induced vasodilation with dipyridamole. This was associated with a marked increase in minimal myocardial vascular resistance with β-blockade, whereas this remained unchanged by ACE inhibition with corresponding findings regarding the structure of subcutaneous small arteries. Furthermore, during both treatments, there was a close relation between resting and hyperemic myocardial vascular resistance, suggesting that improvement in coronary reserve requires reduction in resting vascular resistance.

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**Figure 2.** Individual measurements of (A) resting and (B) dipyridamole-induced myocardial perfusion in controls and patients with hypertension before and after 1 year of treatment. ∗P<0.01 for controls vs pooled patient data at baseline. For further statistical analysis, see Table 2.
observation suggests that changes in LV mass alone may not be important for myocardial vascular resistance.

Previous studies have shown that MP closely correlates to the RPP in healthy individuals. We have now demonstrated that this also applies to hypertensive patients, indicating that the increased myocardial workload associated with hypertension demands an increased perfusion to meet oxygen requirements. Both perindopril and atenolol reduced resting MP, but the reduction was associated with a simultaneous reduction in the RPP demonstrated by a linear correlation between RPP and MP. Thus, based on these results, neither of the treatments seems to affect the relation between myocardial workload and oxygen consumption.

As vascular smooth muscle tone is reduced by dipyridamole, hyperemic vascular resistance will approach the minimal vascular resistance, which is mainly determined by the resistance vascular structure. Thus, the increased myocardial vascular resistance reported in several studies of hypertensive patients was confirmed in the present study and suggests the presence of structural abnormalities in the myocardial circulation. Furthermore, our finding that perindopril, as opposed to atenolol, reduced hyperemic vascular resistance and increased coronary reserve indicates an improvement in myocardial vascular structure consistent with our observations in the subcutaneous arteries. The linear correlation between resting and hyperemic myocardial vascular resistance obtained during treatment suggests that the findings from the peripheral circulation also apply to the myocardial circulation, although changes in media-to-lumen ratio in subcutaneous arteries could not be directly related to changes in myocardial vascular resistance. Taken together, improvement in coronary reserve in hypertensive patients seems to require a therapeutic regimen resulting in reduction in resting myocardial resistance through vasodilation.

Only 6 published studies have investigated the effect of antihypertensive treatment on MP. Two of these used the PET technique, whereas 4 studies used the argon gas chromatography technique. However, using the latter invasive procedure only allows investigation of hypertensive patients with symptoms of ischemia, whereas the PET technique permits investigations of asymptomatic patients, who constitute the majority of the hypertensive population. Furthermore, all studies had in common that antihypertensive treatment was withdrawn before the second measurement of MP. This difference in study design could explain some discrepancies between our and previous investigations. However, we know from previous PET studies that acute \(\beta\)-blockade and acute treatment with perindopril increases dipyridamole-induced hyperemia. Thus, the difference in dipyridamole-induced hyperemia between chronic \(\beta\)-blockade and ACE inhibition found in the present study seems to not be caused by a direct pharmacological effect of the drugs.

**Study Limitations**

MP was measured 8 minutes after commencing the dipyridamole infusion. Because the time to maximal vasodilation may differ between individuals, the fixed time delay may slightly underestimate hyperemic MP. Using the echo Doppler technique for measurement of coronary flow velocity, the effect of higher dipyridamole doses has been tested, and slightly higher flows could be obtained. However, when measured with the PET technique, MP cannot be further enhanced by higher doses of dipyridamole. Thus, our finding of a reduced vasodilator capacity during beta-blockade seems not related to an insufficient dipyridamole dose.

As outlined, change in vascular structure seems a plausible explanation for our findings, but functional factors may also contribute. Dipyridamole acts mainly through inhibition of cellular adenosine reuptake, thereby increasing adenosine concentration, resulting in vasodilation. We have previously shown that myocardial vasodilation to adenosine is partly dependent on endothelial function because it is attenuated by inhibition of nitric oxide synthase. Thus, dipyridamole-induced hyperemia is partly dependent on an intact endothelial function, and endothelial dysfunction may attenuate vasodilation irrespective of any structural vascular changes.
Furthermore, α-adrenergic receptors are present in the coronary microcirculation and increased activity of the sympathetic nervous system, induced by generalized diprydamole-induced vasodilation, may lead to opposing vasoconstriction. This could be more pronounced during β-blockade, because β-receptor–mediated coronary vasodilation is partly inhibited. However, even though we cannot rule out contribution from vasoactive factors limiting diprydamole-induced hyperemia, our results still suggest a reduction in vasodilatory capacity during β-blockade of potential clinical relevance.

**Perspectives**

Despite similar BP reduction, the study indicates benefits regarding coronary reserve and hyperemic MP with ACE inhibition compared with β-blockade in essential hypertensive patients. Whether this is associated with a better clinical outcome in terms of cardiovascular events remains to be demonstrated. However, in addition to BP reduction, improvement in the abnormal vascular structure and left ventricular hypertrophy seems to be an appropriate therapeutic goal, and the present study has suggested benefits of vasodilator therapy regarding MP.

**Acknowledgments**

This work was supported by grants from Institut de Recherches Internationales Servier and the Danish Heart Foundation. M.J.M. has support from the Danish Medical Research Council.

**References**

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_Hypertension_. 2004;44:465-470; originally published online August 23, 2004;
doi: 10.1161/01.HYP.0000141273.72768.b7

_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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