Prostaglandin I$_2$ Contributes to the Vasodepressor Effect of Baicalein in Hypertensive Rats

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Abstract—Lipoxygenase inhibitors reduce blood pressure in hypertensive rats. The vasodepressor effect of lipoxygenase inhibitors may be related to increased production of prostaglandin (PG) I$_2$ since lipoxygenase-derived fatty acid hydroperoxides inhibit PGI$_2$ synthase. This hypothesis was examined in rats made hypertensive by infusion of angiotensin II (200 ng/min IP) for 12 to 14 days. In hypertensive but not in normotensive rats, the lipoxygenase inhibitor baicalein (60 mg/kg SC) increased (P<.05) the conversion of exogenous PGH$_2$ to PGI$_2$ by aortic segments, the release of 6-keto-PGF$_{1a}$ by aortic rings, the concentration of 6-keto-PGF$_{1a}$ in blood, and the renal excretion of 6-keto-PGF$_{1a}$. Treatment with baicalein did not affect the blood pressure of normotensive rats but decreased the blood pressure of hypertensive rats from 177±8 to 133±9 mm Hg after 120 minutes (P<.05). Also, the lipoxygenase inhibitor cinnamyl-3,4-dihydroxy-α-cyanocinnamate (8 mg/kg SC) was without effect on the blood pressure of normotensive rats but decreased the blood pressure of hypertensive rats from 182±4 to 139±8 mm Hg (P<.05). However, the blood pressure of hypertensive rats pretreated with indomethacin (5 mg/kg IV) was affected by neither baicalein nor cinnamyl-3,4-dihydroxy-α-cyanocinnamate. Moreover, in hypertensive rats in which baicalein had decreased blood pressure to 148±6 mm Hg, the administration of rabbit serum containing antibodies against 5,6-dihydro-PGI$_2$ (0.3 mL IV) partially reversed the response to baicalein, increasing blood pressure to 179±7 mm Hg within 20 minutes (P<.05). The antibodies also were shown to block the vasodepressor effect of PGI$_2$ but not of PGE$_2$. Collectively, these data suggest contribution of PGI$_2$ to the acute antihypertensive effect of baicalein in rats with angiotensin II–induced hypertension. (Hypertension. 1998;31:866-871.)

Key Words: angiotensin II | prostaglandin I$_2$ | prostacyclin synthase | 12-lipoxygenase | lipoxygenase inhibitors

Vascular tissues contain a lipoxygenase that catalyzes the oxygenation of C12 of arachidonic acid. The product of this reaction is 12-HPETE, which undergoes spontaneous or peroxidase-catalyzed reduction to 12-HETE. Both 12-HPETE and 12-HETE are capable of influencing vascular functions. 12-HPETE inhibits vascular PGI$_2$ synthase activity and was reported to increase the expression of arachidonic acid–induced, PGH$_2$–mediated constrictor responses in rings of rat aorta. 12-HETE was shown to depolarize renal arterial smooth muscle cells, increase the protein content of cultured porcine aortic smooth muscle cells, and facilitate the stimulatory actions of Ang II and vasopressin on calcium transients in cultured smooth muscle.

Several studies indicate that Ang II promotes lipoxygenase-catalyzed production of eicosanoids in vascular tissue. For example, Ang II was reported to stimulate release of 12-HETE from rings of porcine aortic smooth muscle cells, and facilitate the stimulatory actions of Ang II and vasopressin on calcium transients in cultured smooth muscle.

Reports that lipoxygenase inhibitors attenuate the vascular actions of Ang II and lower blood pressure in hypertensive rats incriminate lipoxygenase-derived eicosanoids in the mechanisms of arterial hypertension. Because 12-HPETE and other hydroperoxides arising from polyunsaturated fatty acids via metabolism by lipoxygenase(s) inhibit PGI$_2$, excessive expression of lipoxygenase or lipoxygenases may promote elevation of blood pressure by weakening the activity of antihypertensive mechanisms mediated by PGI$_2$. If so, lipoxygenase inhibitors may lower blood pressure in such settings by fostering production of PGI$_2$. Therefore, the present study was designed to test the hypothesis that PGI$_2$ participates in the implementation of the antihypertensive effect of the lipoxygenase inhibitor baicalein in rats with Ang II–induced hypertension.

Methods

Animals

Male Sprague-Dawley rats (Charles River Labs) weighing 275 to 300 g were used in all the experiments. The animals were housed in group cages or in individual cages as appropriate and were fed a standard chow (Ralston Purina). All protocols were approved by the Institutional Animal Care and Use Committee.

Experiments were conducted on untreated normotensive rats, sham-infused normotensive rats, and rats with Ang II–induced hypertension. Rats with Ang II–induced hypertension were prepared as previously described. Briefly, an Alzet osmotic minipump (model 2002, Alza Corporation) filled with Ang II ([Ile$^5$]Ang II; Sigma Chemical) was placed through a 1-cm midline incision in the abdominal cavity of rats anesthetized with methoxyflurane (Pitman-Moore); the nominal infusion rate of Ang II was 200 ng/min. Sham-infused rats were prepared by placing in

Received August 25, 1997; first decision September 22, 1997; revision accepted October 31, 1997.

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the abdominal cavity an osmotic minipump filled with 0.01 mol/L acetic acid, the vehicle of Ang II.

Animals in protocols 1, 2, and 3 were instrumented with a chronic arterial catheter. One day before minipump placement, rats were anesthetized with pentobarbital sodium (60 mg/kg IP) and a polyethylene cannula (PE-50) filled with saline solution (0.15 mol/L NaCl) containing heparin (100 units/mL) was introduced through the left femoral artery and advanced into the lower abdominal aorta. Animals in protocols 2 and 3 also were fitted with a venous cannula (PE-50) introduced through the left femoral vein and advanced into the lower inferior vena cava. Both cannulas were tunneled subcutaneously to an exit point at the nape of the neck and plugged with steel pins until use. All rats received ampicillin (30 mg · kg⁻¹ · 12 h⁻¹ SC) for 3 days after surgery.

Experiments were conducted 12 to 14 days after minipump placement. In protocols 1, 2, and 3, the mean arterial pressure of awake rats was measured via the femoral arterial cannula by means of a pressure transducer (model P23XL; Statham Division, Gould Inc) coupled to a polygraph (model 7D; Grass Instrument). In protocol 4, systolic blood pressure was determined through tail sphygmonanometer (Narco Bio-System).

Experimental Protocols

Protocol 1 was designed to examine the effect on blood pressure of treatment with lipoygenase inhibitors baicalein or CDC. 🅺괄研究院). On the day of the experiment, 12 to 14 days after minipump placement, rats with Ang II–induced hypertension were injected subcutaneously with baicalein (60 mg/kg; n=8), CDC (8 mg/kg; n=6), or vehicle alone (2.0 mL/kg of body wt; n=8). Blood pressure was recorded as picomoles of 6-keto-PGF₁α from rings of descending thoracic aorta, conversion of exogenous PGI₂ to PGI₁ by rings of descending thoracic aorta, concentration of prostanoids in venous blood, and renal excretion of 12-HETE and prostanoids. On the day of the experiment, sham-infused rats and rats with Ang II–induced hypertension were injected with baicalein (n=6) or vehicle only (n=6) as described in protocol 1. One hour later, the rats were anesthetized with pentobarbital sodium (60 mg/kg IP), the abdominal cavity was exposed through a midline incision, the inferior vena cava was punctured with an 18-gauge needle to sample blood (1 ml) for measurement of prostanoids, and the descending thoracic aorta was excised and cut into ring segments (3 mm in length). The aortic rings were used immediately to assess release of 6-keto-PGF₁α and ability to convert exogenous PGI₂ to PGI₁.

In additional experiments, rats with Ang II–induced hypertension of 12 days’ duration were housed in metabolic cages and subsequently injected with baicalein (n=8) or vehicle only (n=8) as described in protocol 1. Thereafter, urine was collected for 3 hours to measure renal excretion of prostanoids and 12-HETE. Similar experiments were conducted in sham-infused normotensive rats injected with baicalein (n=6) or vehicle (n=7).

Analytical Procedures

Measurement of 6-Keto-PGF₁α Release by Rings of Thoracic Aorta

Aortic rings were incubated in Krebs’ bicarbonate buffer (2.0 mL) containing arachidonic acid (10 μmol/L) for 15 minutes at 37°C in an atmosphere of 95% O₂/5% CO₂. The amount of 6-keto-PGF₁α in the medium, an estimate of PGI₂ release, was analyzed as previously described through enzyme immunoassay of unextracted samples with reagents purchased from Cayman Chemical. The results are expressed as picomoles of 6-keto-PGF₁α released during the 15-minute incubation period per milligram of dry tissue. 6-Keto-PGF₁α could not be detected in samples generated through incubation of aortic rings denatured by heating at 100°C for 5 minutes.

Measurement of Conversion of PGI₂ to PGI₁ by Rings of Thoracic Aorta

Aortic rings were preincubated for 20 minutes at 37°C in Krebs’ bicarbonate buffer gassed with 95% O₂/5% CO₂ containing indomethacin (10 μmol/L) to inhibit cyclooxygenase. The rings were then transferred to 20-mL vials containing fresh buffer (2.0 mL) for incubation at 37°C for 5 minutes in the presence and absence of exogenous PGI₂ (1 μmol/L). The concentration of 6-keto-PGF₁α in the incubation media was measured through enzyme immunoassay of unextracted samples. The concentration of 6-keto-PGF₁α in medium derived from incubation of aortic rings in indomethacin-containing buffer without exogenous PGI₂ was <3% of the concentration in medium derived from incubations carried out in the presence of exogenous PGI₂. Hence, ≥97% of the 6-keto-PGF₁α in the incubation medium with PGI₂ arises from exogenous PGI₂. Results of the conversion of PGI₂ to PGI₁ are expressed as picomoles of 6-keto-PGF₁α formed during a 3-minute incubation per milligram of dry tissue. No conversion of exogenous PGI₂ to PGI₁ could be detected in control incubations using aortic rings denatured by heating at 100°C for 5 minutes. Hence, when cyclooxygenase is inhibited by
indomethacin, the conversion of exogenous PGH₂ to PGI₂ by aortic rings reflects the tissue activity of PGI₂ synthase. 

**Measurement of PGE₂ and 6-Keto-PGF₁α in Blood**

Blood (1 mL) was drawn from the inferior vena cava into a syringe containing 4 mL of ice-cold ethanol and indomethacin (10 µg/mL). The mixture was stored at −20°C for 24 hours, followed by centrifugation at 1500g for 10 minutes, evaporation of the supernatant under a stream of nitrogen, and reconstitution of the residue in 2 mL of 0.1 mol/L formic acid. PGE₂ and 6-keto-PGF₁α in the formic acid solution were further purified with passage through a column of octadecylsilyl silica (Sep-Pak C-18 cartridges; Waters Associates) according to a published procedure, followed by quantification through enzyme immunoassay. The results are expressed as picomoles of eicosanoid per 3 hours.

**Measurements of Eicosanoids in Urine**

The contents of PGE₂, 6-keto-PGF₁α, and 12-HETE in 3-hour urine samples were determined after purification with passage of the samples through a column of octadecylsil silica. PGE₂ and 6-keto-PGF₁α were measured with enzyme immunoassay. 12-HETE was measured by radioimmunoassay using reagents and a protocol provided by PerSeptive Diagnostics. Data on urinary excretion of eicosanoids are expressed as picomoles of eicosanoid per 3 hours.

**Statistical Analysis**

Results are expressed as mean±SEM. ANOVA followed by the Newman-Keuls a posteriori test was applied to the analysis of data on the effect of drugs on blood pressure and for comparisons among rats with Ang II–induced hypertension and sham-infused controls. Data on the effect of baicalein on 6-keto-PGF₁α release from aortic tissue, blood level of prostaglandins, urinary eicosanoid excretion, and vascular conversion of PGH₂ to PGI₂ were analyzed with unpaired Student’s t-test. The null hypothesis was rejected at a level of P<.05.

**Results**

Fig 1 displays data on mean arterial pressure before and after the administration of baicalein or sesame oil vehicle only to sham-infused normotensive rats and rats with Ang II–induced hypertension of 12 to 14 days’ duration. Before treatment, blood pressure was 103±6 and 177±8 mm Hg (P<.05) in sham-infused rats and Ang II–infused rats, respectively. Treatment with baicalein caused blood pressure to fall progressively in rats with Ang II–induced hypertension, reaching a level of 133±9 mm Hg (P<.05) after 120 minutes. In contrast, treatment with baicalein was without effect on blood pressure in sham-infused normotensive rats. Likewise, treatment with CDC did not affect the blood pressure of sham-infused normotensive rats (103±6 and 100±10 mm Hg before and 120 minutes after CDC, respectively) but decreased (P<.05) the blood pressure of rats with Ang II–induced hypertension from 182±4 to 142±10 and 139±8 mm Hg after 60 and 120 minutes, respectively. The administration of drug/vehicle only did not affect the blood pressure of sham-infused normotensive rats or of rats with Ang II–induced hypertension.

The effects of baicalein on mean arterial pressure in rats with Ang II–induced hypertension pretreated and not pretreated with indomethacin are shown in Fig 2. Before baicalein administration, blood pressure was comparable in hypertensive rats pretreated and not pretreated with indomethacin. Treatment with baicalein decreased (P<.05) blood pressure to 132±11 mm Hg in hypertensive rats without indomethacin pretreatment. In contrast, treatment with baicalein had little or no effect on the blood pressure of hypertensive rats pretreated with indomethacin. Like baicalein, the administration of CDC did not affect the blood pressure of hypertensive rats pretreated with indomethacin (176±5 and 177±6 mm Hg before and 120 minutes after CDC, respectively) but decreased (P<.05) the blood pressure of hypertensive rats without indomethacin pretreatment from 184±5 to 138±13 and 144±8 mm Hg after 60 and 120 minutes, respectively.

Fig 3 shows a comparison of the effects of nonimmune serum and 5,6-dihydro-PGI₂ antiserum on the blood pressure of rats with Ang II–induced hypertension pretreated with indomethacin. The injection of nonimmune serum did not modify the acute antihypertensive response to baicalein. In contrast, the injection of 5,6-dihydro-PGI₂ antiserum caused blood pressure to increase (P<.05), partially reversing the acute antihypertensive effect of baicalein in the hypertensive rats.

The effects of intravenous bolus injections of PGI₂ (2.0 µg/kg) or PGE₂ (2.0 µg/kg) on the mean arterial pressure of normotensive rats before and after the intravenous administration of 5,6-dihydro PGI₂ antiserum are shown in Fig 4.
the injection of the antiserum, PGI₂ and PGE₂ caused blood pressure to fall promptly by 36±6 and 22±2 mm Hg, respectively, followed by a return to preinjection levels within the next 3 to 4 minutes. After injection of the antiserum, vasodepressor responsiveness to PGI₂ but not to PGE₂ was attenuated (P<.05) for up to 90 minutes.

Fig 5 displays data on the conversion of exogenous PGH₂ to PGI₂ by rings of descending thoracic aorta taken from normotensive and hypertensive rats with and without baicalein treatment. In animals without baicalein treatment, the conversion of PGH₂ to PGI₂ by aortic rings of normotensive rats surpassed (P<.05) that by aortic rings of hypertensive rats. Baicalein treatment of the hypertensive rats increased (P<.05) the conversion of exogenous PGH₂ to PGI₂ by aortic rings, whereas baicalein treatment of normotensive rats did not.

Fig 6 shows data on the release of 6-keto-PGF₁α from the rings of descending thoracic aorta taken from normotensive and hypertensive rats with and without baicalein treatment. In animals without baicalein treatment, the release of 6-keto-PGF₁α from aortic rings incubated in medium containing arachidonic acid was higher (P<.05) in hypertensive than in normotensive rats. Baicalein treatment of the hypertensive rats increased further (P<.05) the release of 6-keto-PGF₁α from aortic rings, whereas baicalein treatment of normotensive rats was without effect.

The Table displays data on blood prostaglandins and urinary excretion of eicosanoids in normotensive and hypertensive rats with and without baicalein treatment. In animals without baicalein treatment, the blood concentration of 6-keto-PGF₁α and the urinary excretion rate of 6-keto-PGF₁α and 12-HETE were higher (P<.05) in hypertensive than in normotensive rats. Baicalein treatment of the hypertensive rats increased further (P<.05) the release of 6-keto-PGF₁α from aortic rings, whereas baicalein treatment of normotensive rats was without effect.

Discussion

The results of the present study demonstrate that treatment with baicalein or CDC lowers blood pressure in rats with Ang II–induced hypertension but not in normotensive rats. The study also demonstrates that the renal excretion of 12-HETE is greater in hypertensive than in normotensive rats and that baicalein treatment of the hypertensive rats reduces urinary and hypertensive rats with and without baicalein treatment. In animals without baicalein treatment, the release of 6-keto-PGF₁α from aortic rings incubated in medium containing arachidonic acid was higher (P<.05) in hypertensive than in normotensive rats. Baicalein treatment of the hypertensive rats increased further (P<.05) the release of 6-keto-PGF₁α from aortic rings, whereas baicalein treatment of normotensive rats was without effect.

The Table displays data on blood prostaglandins and urinary excretion of eicosanoids in normotensive and hypertensive rats with and without baicalein treatment. In animals without baicalein treatment, the blood concentration of 6-keto-PGF₁α and the urinary excretion rate of 6-keto-PGF₁α and 12-HETE were higher (P<.05) in hypertensive than in normotensive rats. Baicalein treatment of the hypertensive rats increased further (P<.05) the release of 6-keto-PGF₁α from aortic rings, whereas baicalein treatment of normotensive rats was without effect.

Discussion

The results of the present study demonstrate that treatment with baicalein or CDC lowers blood pressure in rats with Ang II–induced hypertension but not in normotensive rats. The study also demonstrates that the renal excretion of 12-HETE is greater in hypertensive than in normotensive rats and that baicalein treatment of the hypertensive rats reduces urinary
12-HETE excretion to levels not different from those in normotensive rats, which is in agreement with reports that the drug inhibits lipoxygenase(s). These findings are consistent with involvement of products of lipoxygenase activity in the mechanisms underlying Ang II–dependent hypertension in rats. This conclusion also receives support from reports that Ang II promotes vascular expression of 12-lipoxygenase, tissue production of lipoxygenase products is increased in models of Ang II–dependent hypertension, and lipoxygenase-derived eicosanoids contribute directly or indirectly to the vascular actions of Ang II.

The acute antihypertensive effect of baicalein and CDC in rats with Ang II–induced hypertension may be a functional consequence of diminished production of lipoxygenase-derived eicosanoids that mediate or facilitate vasoconstrictor mechanisms. It also may be linked to activation of a vasodilatory mechanism mediated by PGJ2 and/or to deactivation of a pressor mechanism mediated by PGH2, both of which are events caused by elimination of the inhibitory influence of 12-HPETE and other lipoxygenase products on prostacyclin synthase. This study demonstrates that baicalein and CDC do not reduce the blood pressure of hypertensive rats pretreated with indomethacin. Because indomethacin inhibits cyclooxygenase without affecting the vascular production of lipoxygenase-derived HETEs, our results suggest that the acute antihypertensive effect of these agents in rats with Ang II–induced hypertension relies on its implementation on a prostanoid-mediated mechanism. This conclusion derives additional support from experiments demonstrating that the vasodepressor effect of baicalein in hypertensive rats is reversed partially through treatment with 5,6-dihydro-PGI2, anisotserum. The administration of 5,6-dihydro-PGI2 anisotserum also attenuates vasodepressor responsiveness to PGE2 but not to PGE3, which is in agreement with a report that antibodies directed to 5,6-dihydro-PGI2 bind and neutralize the biological activities of PGI2. The observation that 5,6-dihydro-PGI2 anisotserum causes partial reversal of the antihypertensive effect of baicalein implicates PGI2 in the implementation of such an effect.

Previous reports show that vascular and renal production of PGI2 are increased in rats with Ang II–dependent hypertension. In concordance with such studies, we found that rats made hypertensive through infusion of Ang II feature increased circulating levels of 6-keto-PGF1α, elevated urinary excretion of 6-keto-PGF1α, and enhanced release of 6-keto-PGF1α from rings of thoracic aorta during incubation in medium containing arachidonic acid. Paradoxically, the ability of aortic rings to metabolize exogenous PGH2 to PGI2 was reduced in rats with Ang II–induced hypertension, implying that vascular PGI2 synthase activity is reduced in the hypertensive rats. In these animals, the increased release of 6-keto-PGF1α from aortic rings may be linked to overproduction of PGH2, with the resulting elevation in cellular PGH2 concentration driving up PGI2 production in the face of reduced PGI2 synthase activity.

A major finding in this study is that the antihypertensive effect of baicalein in rats with Ang II–induced hypertension is accompanied by an increase in the rate of conversion of exogenous PGH2 to PGI2 by aortic rings, bringing it up to the rate of conversion found in aortic rings from normotensive rats. Previously, it was reported that rings of thoracic aorta taken from rats with aortic coarctation–induced hypertension are impaired in their ability to convert exogenous PGH2 to PGI2 and that this impairment is corrected through exposure of the rings to baicalein or CDC. The notion that baicalein promotes metabolism of PGH2 to PGI2 in models of Ang II–dependent hypertension fits well with our findings that baicalein treatment of hypertensive rats increases the release of 6-keto-PGF1α from aortic segments incubated in medium containing arachidonic acid, the concentration of 6-keto-PGF1α in blood, and the renal excretion of 6-keto-PGF1α. These effects of baicalein are not driven by mechanisms that promote formation of all prostanoids because baicalein treatment of hypertensive rats elicited reduction of blood PGE2 levels and did not affect the renal excretion of PGE2.

It is unlikely that baicalein stimulates PGI2 synthase directly because its administration to normotensive rats did not increase the conversion of PGH2 to PGI2 by aortic rings or increase the release of 6-keto-PGF1α from aortic rings incubated with arachidonic acid, the blood concentration of 6-keto-PGF1α, or the renal excretion of 6-keto-PGF1α. The effects of baicalein on the status of PGI2 formation and levels in rats with Ang II–induced hypertension may be the result of interference with the production of endogenous factors capable of disrupting the metabolism of PGH2 to PGI2 by PGI2 synthase. In this context, reports that PGI2 synthase is inhibited by 12-HPETE and other hydroperoxides derived from polyunsaturated fatty acids via metabolism by lipoxygenase are particularly significant.
Because Ang II stimulates expression of 12-lipoxygenase, the administration of lipoxygenase inhibitors baicalein or CDC to rats with Ang II–induced hypertension may promote vascular conversion of PGI₂ to PGF₁α by minimizing the formation of lipoxygenase-derived fatty acid hydroperoxides.

Recent studies revealed that superoxide anion production is increased in arteriolar vessels of rats with Ang II–induced hypertension. It is also known that prostacyclin synthase is susceptible to inhibition or inactivation by reactive oxygen species and that flavonoids, such as baicalein, and hydroxycinnamic acid derivatives, such as CDC, possess antioxidant properties. Accordingly, these lipoxygenase inhibitors also prevent effects of baicalein in rats with Ang II–induced hypertension by scavenging oxygen radicals that are damaging to prostacyclin synthase.

In summary, we found that baicalein and CDC lower blood pressure in rats made hypertensive by long-term Ang II infusion but not in normotensive rats. The antihypertensive effect of these lipoxygenase inhibitors was prevented through pretreatment with indomethacin. The antihypertensive effect of baicalein was partially reversed by the administration of 5,6-dihydro-PGI₂ antiserum, which blocks PGI₂ and blocks its vasodepressor action. Treatment of the hypertensive rats with baicalein also caused selective increases in the rate of conversion of exogenous PGI₂ to PGF₁α by aortic rings, release of 6-keto-PGF₁α from aortic rings, concentration of 6-keto-PGF₁α in blood, and renal excretion of 6-keto-PGF₁α. These data suggest a contribution of PGI₂ to the acute antihypertensive effect of baicalein in rats with Ang II–induced hypertension. A vasodepressor prostanioid also appears to contribute to the antihypertensive effect of CDC in rats with Ang II–induced hypertension. Baicalein and CDC may promote PGI₂ formation by interfering with the production of one or more inhibitors of PGI₂ synthase, including lipoxygenase–derived fatty acid hydroperoxides and reactive oxygen species.

Acknowledgments

This work was supported by grants 5-PO1-HL-4300 and HL-18579 from Brandeis University for donating the 5,6-dihydro-PGI₂ antiserum used in these studies. We also thank Chiara Kimmel-Preuss and Jennifer Brown for secretarial assistance.

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_Hypertension_. 1998;31:866-871
doi: 10.1161/01.HYP.31.3.866

_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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