Pressor Responses to Norepinephrine During Captopril In Renal Prehypertensive Rabbits

DEBRA G. KOIVUNEN, M.D., J. ALAN JOHNSON, PH.D., W. KIRT NICHOLS, M.D., DAVID W. ZEIGLER, M.S., SUWAN SIRIPAISARNPIT, PH.D., AND CHARLES G. PAYNE, M.S.

SUMMARY The role of angiotensin II (All) in pressor hyperresponsiveness was examined in conscious one-kidney, one clip rabbits with renal artery stenosis on 3-days' duration (renal prehypertensive rabbits). Conscious one-kidney rabbits without renal artery stenosis served as controls. Two experiments were performed. The first experiment used four groups of six rabbits each, to examine the pressor responses to intravenous (i.v.) infusions of norepinephrine (NE) at several doses, ranging from 25 to 1200 ng/min/kg body weight, in 3-day renal artery stenosis and in 3-day control rabbits, receiving NE plus the angiotensin-converting enzyme inhibitor, captopril (SQ 14,225), or receiving NE alone. The arterial pressure and values for plasma renin activity (PRA) were the same in the renal artery stenosis rabbits as in the controls. The exaggerated pressor responses to NE in the renal artery stenosis rabbits were restored to normal by captopril administration.

The second experiment investigated the pressor responses to i.v. infusions of NE at 800 ng/min/kg in six rabbits with renal artery stenosis and in six control rabbits before captopril, during captopril administration, and during the administration of captopril plus the i.v. infusion of All at 0.5, 1.0, and 2.0 ng/min/kg body weight. Plasma concentrations of All were determined at each point in this experiment. The renal artery stenosis rabbits had the same values for arterial pressure and PRA as the control rabbits. The renal artery stenosis rabbits had increased pressor responses to NE, and this pressor hyperresponsiveness was abolished by captopril. The i.v. infusion of All during captopril treatment in the renal artery stenosis rabbits increased the pressor responses to NE, and All infusion at 2.0 ng/min/kg completely restored the pressor hyperresponsiveness in these rabbits. The control rabbits had no changes in the pressor responses to NE with captopril or with captopril plus any of the All doses. Before captopril, the control and renal artery stenosis rabbits had the same plasma concentrations of All. With captopril, plasma concentrations of All in the renal artery stenosis rabbits decreased to undetectably low levels and remained so during the infusions of All at all doses. This study provided strong evidence that plasma All plays an important role in the enhanced pressor responses to NE in 3-day renal artery stenosis rabbits, and that this effect is not due to elevated plasma levels of All. (Hypertension 5: 159-165, 1983)

KEY WORDS • renal artery stenosis • pressor hyperresponsiveness • angiotensin converting enzyme inhibition • angiotensin II • plasma angiotensin II concentrations

EXAGGERATED pressor responses to vasoconstrictor agents have been observed in patients with hypertension as well as in several animal models of experimental hypertension. This pressor hyperresponsiveness occurs prior to the development of hypertension. Pressor hyperresponsiveness is associated with enhanced increases in vascular resistance in hypertensive and prehypertensive animals, suggesting that the arteriolar smooth muscle cells are more responsive to vasoconstrictor agents in these animals. Earlier studies from this laboratory have shown that i.v. infusion of the angiotensin II (All) competitive antagonist, [Sar1, Ile8] All, abolished pressor hyperresponsiveness in renal prehypertensive rabbits. The present study examined the effect of another antagonist of the renin-angiotensin system, the angiotensin-converting enzyme inhibitor, captopril (SQ 14,225), on pressor hyperresponsiveness in prehypertensive rabbits with renal artery stenosis. This study also investigated further the role of plasma All in press-
sor hyperresponsiveness in this model by examining the effects of i.v. infusions of small doses of All on pressor responsiveness in renal prehypertensive rabbits receiving captopril.

**Methods**

Thirty-six male New Zealand white rabbits, weighing from 2.75 to 3.15 kg, were caged individually in a constant environment of 27°C with room lights automatically controlled on a 12-hour on/off cycle. All rabbits were fed a commercial diet (Purina rabbit chow) containing 0.167 mEq of Na⁺ and 0.467 mEq of K⁺ per gram, and water ad libitum.

**Surgical Procedures**

Eighteen rabbits received a unilateral nephrectomy and served as controls; the remaining 18 rabbits received renal artery stenosis plus a contralateral nephrectomy (one-kidney, one clip). Renal artery stenosis was produced by the method of Brooks and Muirhead by placing a silver clip with an internal gap size of 0.6 mm on the left renal artery. These surgical procedures were performed through a ventral midline laparotomy incision under sterile conditions on rabbits anesthetized with 3% to 5% halothane in nitrous oxide and oxygen, administered with a mask. Afterward the rabbits were allowed to recover and were returned to their cages. The acute experiments were performed 3 days later.

On the morning of the 3rd postoperative day, each rabbit again was anesthetized with halothane plus nitrous oxide as before, and polyvinyl catheters (Fr 5 infant feeding tubes) were placed in the lower abdominal aorta and inferior vena cava via the femoral artery and vein. In experiments in which an additional intravenous line was required, a marginal ear vein was cannulated percutaneously with polyethylene (PE 50) tubing. After insertion of the catheters, each rabbit was placed in a rectangular box to restrict its movements and was allowed 5 hours to recover. The acute experiments were performed on conscious rabbits in these boxes, unrestrained except by the size of the box. Two separate experiments were performed.

**Experiment 1: Pressor Responses to Norepinephrine During Captopril**

Four groups of six rabbits each were used in these experiments. The first and second groups consisted of one-kidney control rabbits, and the third and fourth groups were one-kidney rabbits with renal artery stenosis of 3 days' duration. In each group, an arterial blood sample (2 ml) was obtained and placed in a chilled tube containing ethylenediaminetetraacetate (EDTA); this sample was used for the determination of plasma renin activity (PRA). Mean arterial pressure (MAP) was measured through the femoral arterial catheter by a pressure transducer (Statham model P23Db, Oxnard, California) and was recorded on an oscillographic recorder (Hewlett-Packard, model 7754B, Palo Alto, California). After MAP had been recorded for 5 minutes, heart rate was determined by recording pulsatile blood pressure at a fast paper speed (10 mm/sec). The gain of the preamplifier of the recorder was then increased so that a 1 mm pen deflection represented a 1 mm Hg change in arterial pressure, and the pen was positioned near the lower portion of the recording channel by the use of a zero-suppression control; this allowed the accurate recording of small changes in MAP. Each rabbit then received a 5-minute infusion of norepinephrine (NE) (800 ng/min/kg body weight) in 5% dextrose-water, and the pressor response was recorded. The solutions of NE were prepared by diluting a fresh ampule of a commercial solution (Levophed, Winthrop Laboratories, New York, New York) in 5% dextrose-water. Rabbits in Groups 2 and 4 received an i.v. injection of 300 ng of synthetic angiotensin I (AI) in saline (0.30 ml), the pressor responses noted, and a solution of captopril was then infused i.v. through the femoral venous catheter. For the remainder of the experiment, captopril dissolved in 5% dextrose-water was infused at a dose rate of 0.3 mg/min/kg of body weight 5 minutes and then at 0.1 mg/min/kg. In Groups 1 and 3, the solution of 5% dextrose-water was infused without captopril.

In Groups 2 and 4, after 10 minutes of captopril infusion, the pressor response to the i.v. injection of 300 ng of AI again was determined in each rabbit to evaluate the adequacy of the inhibition of the angiotensin-converting enzyme. Then, in each group of rabbits, NE was infused at doses of 25, 50, 100, 200, 400, 800, and 1200 ng/min/kg body weight, and the pressor responses recorded. The MAP during the 1-minute period prior to NE infusion was taken as the control pressure, and the increase in MAP that occurred during 5 minutes of NE infusion was taken as the pressor response. An interval of at least 5 minutes was allowed between infusions, and the next dose of NE was not infused until the MAP had returned to the preinfusion level and stabilized. After infusion of the last NE dose, the pressor response to 300 ng of AI was again determined.

**Experiment 2: Pressor Responses to Norepinephrine During Captopril Plus AI**

This experiment required six one-kidney control rabbits and six one-kidney, 3-day renal artery stenosis rabbits. At the start of Experiment 2, a 5 ml sample of arterial blood was collected for PRA and plasma AI determinations. The 3 ml blood sample for plasma AI concentration was placed in a chilled tube containing EDTA plus 50 μg of captopril. Control measurements of MAP were obtained for 5 minutes, and heart rate was measured in each rabbit as previously described. The gain of the recorder was increased, and the pressor response to NE, infused at 800 ng/min/kg body weight, was determined as in Experiment 1. After cessation of the NE infusion and after the MAP had returned to the control level, the pressor response to an i.v. injection of 300 ng of AI was recorded. Each rabbit then was infused with captopril as in Experiment
1. After 10 minutes of infusion of the angiotensin-converting enzyme inhibitor, a 3-ml blood sample was collected for plasma All concentration. Again, 300 ng of All was injected i.v. while MAP was recorded, to test the adequacy of the inhibition of the angiotensin-converting enzyme. While infusion of captopril was continued, the pressor response to NE at 800 ng/min/kg was determined. A solution of All in 5% dextrose-water was then infused i.v. at 0.5 ng/min/kg body weight, concurrent with the captopril infusion. After 5 minutes of All infusion at this dose, an arterial blood sample (3 ml) again was obtained for plasma All concentration, and the pressor response to NE at 800 ng/min/kg was determined, as previously. The All solution was then changed so as to infuse All at 1.0 ng/min/kg, and 5 minutes later another arterial blood sample was collected for plasma All concentration. Again, the pressor response to an infusion of NE at 800 ng/min/kg was recorded. The All infusion was increased further to 2.0 ng/min/kg, and after 5 minutes of infusion at this dose, an arterial blood sample was collected for determination of plasma All concentration, and again the pressor response to NE (800 ng/min/kg) was obtained. To verify the continued inhibition of angiotensin-converting enzyme, the pressor was obtained for a final i.v. injection of 300 ng of AI. In these experiments, all blood removed was replaced immediately with the same volume of blood from a normal donor rabbit.

Analytical Procedures

Determinations of PRA were by radioimmunoassay (RIA) of generated All, by a modification of the method of Cohen et al, this modification, as performed in our laboratory, has been described previously. Plasma concentrations of All were determined by RIA by a modification of the method described by Gocke et al. Blood samples, collected in chilled tubes containing EDTA plus captopril (20 µg/ml blood), were placed in ice, spun in a refrigerated centrifuge, and the plasma samples were stored frozen at —20°C. Before assay, the samples were thawed in an ice bath, and 0.75 ml of each plasma sample was placed in a small plastic tube. To each tube was added 1.50 ml of absolute ethanol to precipitate the proteins. The tubes were spun, and 200 µl aliquots of the supernatant were pipetted into a series of small plastic tubes, for the assay of endogenous AI and All. The tubes were evaporated to dryness with filtered air and stored at —20°C until assayed. At the time of assay, 125I-All (New England Nuclear) was diluted in a Tris buffer (0.1 M Tris, pH adjusted to 7.4, plus bovine serum albumin, 2.5 mg/ml). Synthetic asp-1, Ile-5 All (Vega Biochemicals) was dried in vacuum for 2 days, and a stock solution of 10,000 ng/ml was prepared in the Tris buffer; dilutions were prepared in a series of tubes to provide a range of standards from 3.9 to 250 pg. The diluted All trace (0.5 ml) was added to each sample and standard tube. Each tube also received 0.5 ml of All antiserum, diluted 1/160,000 in Tris buffer. The All antiserum was produced by the periodic injection of rabbits with All conjugated to serum albumin, together with Freund’s adjuvant. The tubes for the assay of AI likewise received 125I-Al and All antiserum, as in the assay of PRA. Each tube was incubated in an ice bath for 18 hours, and then 1 ml of a solution of dextran-coated charcoal in barbital buffer (pH 7.4) was added to separate the free from the antibody-bound angiotensin. The samples were centrifuged and decanted, and the charcoal pellets (free angiotensin) were counted in a well-type automated gamma counter. The results were calculated from a log-logit transformation of the angiotensin standards vs the ratio of the bound counts of angiotensin for each standard to the bound counts of angiotensin for the zero angiotensin standard. Because AI has approximately a 20% cross-reactivity with the All antiserum, plasma All concentrations were corrected for this. With this method, the recovery of All added to human plasma samples averaged 102% (n = 9) over a range of 75 to 600 pg/ml. Intraassay variation averaged 2.4% (n = 10), based on an average All concentration of 79 ± 5.6 (SD) pg/ml; interassay variation averaged 10.7% (n = 25).

Statistics

In Experiment 1, the control values for MAP, heart rate, PRA, and the pressor responses to each dose of NE were compared among the four groups of rabbits by analysis of variance; when significant values were observed, the data were analyzed further by Duncan’s new multiple range test. In Experiment 2, the values obtained during the control period for MAP heart rate, PRA, plasma All concentration, and the pressor response to NE were compared between the control and 3-day renal artery stenosis groups by Student’s t test for group observations. Changes in MAP, NE pressor responses, and plasma All concentrations with captopril alone and with each All infusion were evaluated within each group by Student’s t test for paired observations.

Results

Experiment 1: Pressor Responses to Norepinephrine During Captopril

The initial values for MAP, heart rate, PRA, and the pressor responses to NE at 800 ng/min/kg are summarized in Table 1. There were no significant differences in MAP, heart rate, and PRA among the four groups. The pressor responses to NE prior to infusion of captopril were significantly (p < 0.01) greater in Groups 3 and 4 (renal artery stenosis groups) than in Groups 1 and 2 (control groups). Figure 1 gives the log-dose response curves for the pressor responses to the various doses of NE for all four groups. The curves represent the best-fit of the data for each group to the equation, y = a(log x)^n, where y is the pressor response, x is the NE dose, and a and n are constants. The pressor responses for the 3-day renal artery stenosis rabbits not receiving captopril (Group 3) were significantly greater than the pressor responses for the other three groups
TABLE 1. Initial Values for Rabbits in Experiment 1

<table>
<thead>
<tr>
<th>Group 1 (controls)</th>
<th>Group 2 (controls)</th>
<th>Group 3 (RAS)</th>
<th>Group 4 (RAS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>93 ± 2</td>
<td>100 ± 3</td>
<td>92 ± 5</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>261 ± 10</td>
<td>229 ± 14</td>
<td>238 ± 9</td>
</tr>
<tr>
<td>Plasma renin activity</td>
<td>6.3 ± 1.0</td>
<td>5.2 ± 0.6</td>
<td>4.8 ± 0.7</td>
</tr>
<tr>
<td>Pressor response to norepinephrine (800 ng/min/kg)</td>
<td>+12 ± 1</td>
<td>+14 ± 2</td>
<td>+22* ± 2</td>
</tr>
</tbody>
</table>

Values are means ± SEM for six rabbits per group. Controls are one-kidney (3-day) rabbits; RAS are one-kidney, one clip (3-day) rabbits. Groups 1 and 3 did not receive captopril; Groups 2 and 4 received captopril subsequent to these measurements.

*p < 0.01, compared with values obtained for the other groups.

at all NE doses. The pressor responses to NE for the other three groups of rabbits were quite similar and were not significantly different from each other. Both groups of rabbits receiving captopril showed a fall in MAP averaging 5 mm Hg each during the infusion, but these decreases were not statistically significant. The pressor responses to 300 ng of Al averaged +16 ± 2 (SEM) and +23 ± 2 mm Hg before captopril for Groups 2 and 4 respectively; no responses to this dose of Al were observed for either group at either time during infusion of captopril.

Experiment 2: Pressor Responses to Norepinephrine During Captopril Plus All

Table 2 gives the initial values for MAP, heart rate, and PRA for the one-kidney (3-day) control and for the one-kidney, one clip (3-day) experimental groups of rabbits. There were no significant differences between these two groups for any of these factors except for pressor responses to NE, which were significantly (p < 0.01) greater in the renal artery stenosis group than in the control group.

Values for the pressor responses to NE in the control and renal artery stenosis groups are summarized in figures 2 and 3, respectively. In the control group (fig. 2), the pressor responses to NE were not altered by captopril nor by infusion of All at the three dose levels during captopril infusion. In the 3-day renal artery stenosis rabbits (fig. 3), however, captopril infusion resulted in a marked and significant (p < 0.01) reduction in the pressor responses to NE. Furthermore, infusion of All during captopril administration increased the pressor responses to NE in a progressive manner with increasing All dose infusion rates until the initial pressor responses to NE were reestablished with All infusions of 2.0 ng/min/kg of body weight.

Plasma All concentrations were successfully determined for five control and five renal artery stenosis rabbits, and are summarized in table 3. Prior to captopril administration, the plasma concentrations of All were very similar between the two groups. Following administration of captopril, the plasma All concentrations in the control rabbits showed a slight decrease, although not statistically significant, and the infusion of All produced slight rises in plasma All levels. In the renal artery stenosis rabbits, however, the administration of captopril resulted in a decrease in plasma All concentrations to undetectably low levels in four of the five rabbits, and plasma All concentrations remained undetectably low during the subsequent infusion of All.

The administration of captopril in this experiment resulted in a slight decrease in MAP, averaging 4 mm Hg for both the control and renal artery stenosis groups of rabbits; these declines were not statistically signifi-
TABLE 2. Initial Values for Rabbits in Experiment 2

<table>
<thead>
<tr>
<th></th>
<th>One-kidney (3-day) control rabbits</th>
<th>One-kidney, one clip (3-day) rabbits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>97 ± 2</td>
<td>95 ± 2</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>240 ± 11</td>
<td>226 ± 11</td>
</tr>
<tr>
<td>Plasma renin activity</td>
<td>4.0 ± 1.9</td>
<td>5.2 ± 1.9</td>
</tr>
<tr>
<td>Pressor response to norepinephrine (800 ng/min/kg)</td>
<td>+12 ± 2</td>
<td>+24* ± 3</td>
</tr>
</tbody>
</table>

Values are means ± sem for six rabbits per group. *p < 0.01, compared to the control group.

cant, however. Infusion of All did not produce any elevations in MAP at any of the three doses in either group of rabbits. The pressor responses to 300 ng of AI prior to captopril averaged +20 ± 4 (sem) and +16 ± 2 mm Hg for the control and renal artery stenosis groups respectively. Following captopril, no pressor responses to this dose of AI were observed.

Discussion

These experiments were performed in conscious rabbits; however, 5 hours prior to an experiment each rabbit was anesthetized with halothane plus nitrous oxide in order to place catheters in the blood vessels. Because halothane is known to produce changes in the circulatory system, the question arises as to whether the 5-hour recovery time allotted was adequate for complete recovery from the effects of this anesthetic agent. Previous studies from this laboratory have shown that rabbits anesthetized with halothane plus nitrous oxide to surgical levels had decreases in arterial pressure and cardiac output, with elevated values for PRA. These studies also demonstrated, however, that after removing the animals from the anesthesia the MAP and cardiac output recovered to preanesthetic values by 15 minutes, and PRA returned to control levels within 210 minutes. Therefore, the 5-hour time allowed following removal from anesthesia until the beginning of the experimental procedures in the present study should have been adequate for the rabbits to recover fully from the effects of the short-term anesthetization with halothane.

There is considerable evidence that All in subpressor doses in normal animals will enhance the vasoconstrictor effects of NE or of sympathetic nerve stimulations. Studies by Khairallah et al. and by Sakurai and Hashimoto have demonstrated that in isolated perfused rabbit ears the addition of All to the

FIGURE 2. Pressor responses to norepinephrine (800 ng/min/kg body weight) at the beginning of the experiment (first open bar), during captopril (SQ 14,225) (second open bar), and during captopril plus angiotensin II (A-II) infusions at 0.5, 1.0, and 2.0 ng/min/kg body weight (shaded bars) in one-kidney (3-day) control rabbits. Bars represent means ± sem for six rabbits. There were no statistical differences between any of these pressor responses.
The renal artery stenosis group, and with the i.v. infusion of AII at 2.0 ng/min/kg by weight, a dose of AII that completely restores pressor hyperresponsiveness in these rabbits, the plasma levels of AII were still below the minimal detectable level of the assay. Thus, although AII appears to be necessary for pressor hyperresponsiveness to occur in this renal artery stenosis model, only very small amounts of AII are required to promote this phenomenon. These findings support the hypothesis that increased receptor binding of AII is involved in mediating pressor hyperresponsiveness in these renal prehypertensive rabbits. The observation in this study that captopril administration resulted in a greater decrease in plasma AII concentrations in the 3-day renal artery stenosis rabbits than in the normal rabbits is in keeping with this hypothesis of increased AII binding in this renal artery stenosis model.

Kikta and Fregly, 25 studying the contractility of aortic rings from normal rats, reported that the degree of contractility of the rings in response to NE and to phenylephrine was diminished by captopril; they conclude that captopril depresses alpha-adrenergic responsiveness in vascular smooth muscle similarly, Okuno et al. 26 found that captopril decreased the contractile responses to NE in perfused mesenteric vascular beds of normal rats. From these studies it could be surmised that the decreased pressor responses to NE infusions produced by captopril in the renal artery stenosis rabbits in the present study may have been due to an effect of captopril on adrenergic receptors, independent of its effect to block angiotensin conversion. However, the present study found no effect of captopril on the pressor responses to NE in normal rabbits; similarly, Murthy et al. 27 found no alterations in the pressor responses to NE in normal conscious rabbits after the administration of captopril. Furthermore, the observation that the infusion of AII in low doses restored pressor hyperresponsiveness to NE in captopril-treated rabbits with renal artery stenosis provides further evidence that captopril does not diminish the pressor response to NE in this rabbit model by a direct effect on adrenergic receptors of arteriolar smooth muscle cells. This observation also indicates that the decreased pressor responses to NE that occurred following captopril administration in the renal artery stenosis rabbits did not result from the bradykinin-potentiating activity of captopril nor from any direct action of captopril on the arterioles.

It has been reported that AII may be produced in certain localized areas of the body. There is considerable evidence for the presence of a functional renin-angiotensin system in the brain. 28 Also, Malik and Nasjletti 29 have provided evidence that renin located within the vascular walls of isolated mesenteric arteries from normal rats has the capability of producing AII in amounts sufficient to potentiate the vasoconstrictor effects of NE or of sympathetic nerve stimulation. In studies from our laboratory, because pressor hyperresponsiveness in renal prehypertensive rabbits was abolished by agents that block the renin-angiotensin system despite the consistent finding of normal
values for PRA and the finding of normal values for plasma All concentrations, it would seem plausible that All produced in some localized area, rather than All that is in the plasma, may be the All involved in mediating the pressor hyperresponsiveness in this model. However, the results of the present study demonstrated that pressor hyperresponsiveness following captopril in 3-day renal artery stenosis rabbits was restored by the i.v. infusion of a low dose of All. Because this restoration of pressor hyperresponsiveness occurred with infusion of All into the circulatory system, these results implicate plasma All and not locally-produced tissue All as the source of the All involved in mediating pressor hyperresponsiveness in this model.

Acknowledgments

The authors are very grateful to James Kohrs for performing the assays for plasma angiotensin II concentration and to Dan Cosby for performing the assays for plasma renin activity. The captopril (SQ 14,225) used in this study was generously provided by The Squibb Institute for Medical Research, Princeton, New Jersey.

References


PRESSOR RESPONSES IN RABBITS/Koivunen et al. 165

Downloaded from http://hyper.ahajournals.org/ by guest on September 23, 2017
Pressor responses to norepinephrine during captopril in renal prehypertensive rabbits.
D G Koivunen, J A Johnson, W K Nichols, D W Zeigler, S Siripaisarnpipat and C G Payne

Hypertension. 1983;5:159-165
doi: 10.1161/01.HYP.5.2.159

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1983 American Heart Association. Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/5/2/159.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/