Nitric Oxide Participates in Calcium-Mediated Regulation of Renin Release

William H. Beierwaltes

Abstract The regulation of renin release is unusual in that intracellular calcium reportedly acts as an inhibitory second messenger. Increased calcium not only inhibits renin release but is a cofactor in nitric oxide synthesis. Also, nitric oxide can inhibit renin release. This study was done in vitro using rat renal cortical slices to determine whether calcium-mediated renin inhibition could be in part due to the concurrent production of nitric oxide. Renin concentration in the incubation medium was determined by radioimmunoassay for angiotensin I (Ang I) generation (in nanograms Ang I per hour per milligram per 30 minutes of incubation). In all studies, n=6 to 17. In normal-calcium incubation medium (2.6 mmol/L), 10\(^{-4}\) mol/L N\(^\circ\)-monomethyl L-arginine, which blocks nitric oxide synthesis, caused an 18% increase in basal renin release (78.6±8.9 versus 66.7±5.8 [ng Ang I/h]/mg per 30 minutes incubation, \(P<.05\)). When calcium was eliminated from the incubation medium, basal renin release doubled (to 133.1±15.2 [ng Ang I/h]/mg per 30 minutes incubation, \(P<.001\)). Without calcium, inhibiting nitric oxide synthesis had no further effect on renin release (126.8±17.7 [ng Ang I/h]/mg per 30 minutes incubation). High-calcium medium (7.8 mmol/L) reduced basal renin release by half (30.8±4.8 [ng Ang I/h]/mg per 30 minutes incubation, \(P<.001\)), but inhibiting nitric oxide synthesis in high-calcium medium stimulated renin release by 50% (46.9±6.2 [ng Ang I/h]/mg per 30 minutes incubation, \(P<.005\)). Addition of the calmodulin inhibitor W-7 completely reversed the inhibition of renin by high-calcium medium. Incubation of cortical slices with angiotensin II also resulted in a 45% suppression of basal renin release (\(P<.005\)), and this effect could be blocked by either removal of calcium from the incubation medium or inhibition of nitric oxide synthesis. Thus, nitric oxide synthesis inhibition increased basal renin release in proportion to the amount of calcium in the incubation medium. Furthermore, angiotensin inhibited renin by a calcium- and apparently a nitric oxide-dependent pathway. Because nitric oxide can inhibit renin release, these results suggest that at least part of the inhibitory influence of calcium on renin release can be attributed to calcium-dependent nitric oxide synthesis. (Hypertension. 1994;23[suppl I]:I-40-I-44.)

Key Words • renin • endothelium • nitric oxide • calcium • calmodulin • guanosine cyclic monophosphate • isoproterenol

Calcium serves as a ubiquitous intracellular signal transducer. The constitutive synthesis of nitric oxide (NO) from the endothelium requires calcium and calmodulin as cofactors.\(^1\)\(^2\) Stimulation of NO is dependent on an influx from extracellular calcium, reportedly through some non-voltage-dependent calcium channel.\(^3\) Agents that stimulate endothelial NO synthesis in vitro have also been shown to increase the intracellular calcium concentration.\(^4\) Thus, calcium seems to be an important intracellular mediator of endothelial NO synthesis.

NO has been shown to inhibit the release (or secretion) of renin both in vitro\(^5\)\(^6\) and in vivo.\(^7\)\(^8\) This is apparently due to NO synthesis in the endothelium of the afferent arteriole, which permeates the modified smooth muscle cells of the juxtaglomerular apparatus. Here, it stimulates guanylate cyclase to form the renininhibiting second messenger cyclic guanosine monophosphate (cGMP).\(^6\)\(^9\)\(^11\)

Contrary to most intracellular signaling mechanisms, the release of renin is inhibited by increased intracellular calcium,\(^12\) and in vitro, agents that inhibit renin release also require extracellular calcium. Park et al\(^13\) have shown in vitro an inverse relation between the intracellular calcium concentration and the release of renin and that intracellular calcium at normal or elevated levels inhibits renin release through a calmodulin-mediated process. However, the subsequent components of the inhibitory cascade induced by increasing intracellular calcium are not yet defined.

Because increasing intracellular calcium both stimulates NO synthesis and inhibits renin release using in vitro preparations from the renal cortex and NO also inhibits renin, it seemed a logical hypothesis that at least part of the inhibitory effect of calcium on renin release is due to calcium-dependent NO synthesis and the subsequent inhibitory influence of NO (presumably through cGMP-mediated inhibition of renin).

To test this hypothesis, in vitro experiments were carried out with the use of rat renal cortical slices based on the techniques and observations previously used to show inhibition of renin by both calcium and calmodulin\(^13\) and by NO synthesis.\(^3\) The combined results support the possibility that at least part of the inhibition of renin by stimuli that increase intracellular calcium may be attributed to inhibition via the concurrent stimulus of NO synthesis.

Methods

All the studies were performed with an in vitro preparation incubating renal cortical slices as previously described.\(^14\) Briefly, male Sprague-Dawley rats (Charles River Laboratories Inc, Wilmington, Mass) of 250 to 350 g body weight were fasted overnight and then anesthetized by intraperitoneal

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sodium pentobarbital (Nembutal, Abbott Laboratories, Chicago, Ill; 5 mg/100 g body wt). The kidneys were flushed free of blood by retrograde perfusion through a cannula placed in the aorta distal to both renal arteries. All procedures were in accordance with our institutional guidelines and approved by the Institutional Animal Care and Use Committee.

Incubations were carried out using the bicarbonate buffer medium of Churchill and Churchill,15 which contains (mmol/L) NaCl, 125; NaHCO3, 19; KCl, 4; CaCl2, 2.6; NaH2PO4, 1.2; MgSO4, 0.8; as well as 0.2 g/100 mL glucose. It was equilibrated with a mixture of 95% O2 and 5% CO2 to a pH of 7.4 at a temperature of 37°C. Two 500-μm slices were cut from each lateral surface of decapsulated kidneys with a Stadie-Riggs microtome. Slices from each half were paired for concurrent control and experimental incubations; they were rinsed, blotted, and placed into a 25-mL Erlenmeyer flask in 10 mL of medium containing 0.1 g/100 mL heat-inactivated bovine serum albumin (Difco Laboratories, Detroit, Mich). The flasks were continuously gassed with 95% O2-5% CO2 at 37°C and shaken at approximately 1 revolution per second in a Precision water bath (GCA, Chicago, Ill). After 30 minutes of equilibration, a 200-μL aliquot was taken for assay of renin concentration. The experimental agent or its vehicle was then added, and after an additional 30 minutes a second 200-μL aliquot was sampled. Samples were centrifuged and frozen for later analysis. The slices were oven-dried and weighed to correct results by milligrams of dry weight. Renin release was determined as the difference in concentration between collections obtained at 30 and 60 minutes of incubation.

The following pharmaceutical tools were used to carry out the proposed studies: Calcium-mediated inhibition of renin release was done by altering the extracellular calcium to concentrations of 0, 2.6, or 7.8 mmol/L or by addition of 10^-4 or 10^-6 mol/L angiotensin II. Zero-calcium medium was ensured by the addition of 10^-3 mol/L EGTA (Sigma Chemical Co, St Louis, Mo) to chelate free calcium. NO synthesis inhibition was performed using 10^-4 mol/L N^6-monomethyl L-arginine (L-NMMA, Calbiochem Corp, La Jolla, Calif) as previously reported.5 Calmodulin was inhibited using 5x10^-5 mol/L W-7 [A-\(3\)-{6-aminohexyl}-5-chloro-1-naphthalenesulfonamide, Sigma]. The stimulation of renin through a cyclic AMP-mediated pathway was with 10^-6 mol/L isoproterenol (Aldrich Chemical Co, Milwaukee, Wis).9,10 Experimental protocols are outlined below.

Calcium Concentration and Nitric Oxide Synthesis Inhibition by L-NMMA
To test the role of NO in the calcium-mediated suppression of renin release, cortical slices were incubated in modified buffer medium containing either 0 mmol/L calcium plus EGTA or 2.6 or 7.8 mmol/L calcium. Cortical slices were paired such that they were incubated in low-, normal-, or high-calcium medium either in the presence or absence of the NO synthesis inhibitor L-NMMA. The basal renin release was measured over 30 minutes.

Effect of Inhibition of Nitric Oxide Synthesis and Calmodulin on Renin Release
These experiments were designed to determine to what extent inhibition of renin release by increased extracellular calcium medium was mediated by either NO synthesis or calmodulin. To do this, cortical slices were incubated in normal-calcium medium as a reference. Then, additional incubations using the high-calcium medium were run, either alone or with the addition of L-NMMA, the calmodulin inhibitor W-7, or a combination of the two inhibitors.

Effect of Low Extracellular Calcium on Angiotensin II-Mediated Suppression of Renin Release
The importance of calcium in the angiotensin II-mediated suppression of renin release in this in vitro preparation was tested by comparing renin release from cortical slices in either normal-calcium (2.6 mmol/L) or low-calcium (0 mmol/L plus EGTA) medium. Incubations were run either for basal release or in the presence of 10^-6 mol/L angiotensin II.

Effect of L-NMMA on Angiotensin II-Mediated Suppression of Renin Release
Additional studies were run to determine the extent of NO synthesis inhibition in the angiotensin II-mediated suppression of renin release. Cortical slices were incubated in normal-calcium medium or medium containing L-NMMA. A second, similar paired set of experiments was carried out with the addition of 10^-4 mol/L angiotensin II to the media at 30 minutes.

Isoproterenol-Stimulated Renin Release, Nitric Oxide, and Calmodulin
It has been proposed that cGMP may inhibit cyclic AMP-mediated isoproterenol stimulation of renin release.6 To determine the possible influence of NO or calmodulin in the calcium-mediated suppression of renin release, we incubated cortical slices in normal-calcium medium, in the presence of L-NMMA, or with a combination of L-NMMA and W-7. An additional set of experiments was run using 7.8 mmol/L calcium medium. Cortical slices were incubated with or without the addition of both L-NMMA and W-7. Cortical slices were paired for stimulation from either side of the same kidney; they were incubated as either a time control (basal) or were stimulated at 30 minutes with isoproterenol.

Analytic Methods
Determination of the renin concentration in the buffer medium was by radioimmunoassay for generation of angiotensin I (Ang I) in the presence of excess exogenous rat angiotensinogen after the method of Haber et al16 as previously described.17 Renin concentration was corrected by the dry weight of tissue in milligrams dry weight and is presented in units of nanograms Ang I per hour per milligram per 30 minutes of incubation.

Data are presented as the arithmetic mean±1 SEM. Changes in renin release over time were analyzed by Student’s paired t test, comparing the tested slices with matched controls from the same kidney.5 Comparisons were considered significantly different at a value of P<.05. Comparisons of renin release from different experiments were run using an unpaired Student’s t test.

Results
Calcium Concentration and Nitric Oxide Synthesis Inhibition by L-NMMA
The effect of NO synthesis inhibition on the inhibition of renin release by extracellular calcium concentra-

**TABLE 1. Effect of Nitric Oxide Synthesis inhibition by L-NMMA on Renin Release From Cortical Slices Incubated in Low, Normal, and High Calcium Concentrations**

<table>
<thead>
<tr>
<th>Calcium Concentration</th>
<th>L-NMMA</th>
<th>Basal</th>
<th>L-NMMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 mmol/L Ca^2+ (+EGTA)</td>
<td>Basal</td>
<td>133.1±15.2</td>
<td>66.7±5.8</td>
</tr>
<tr>
<td></td>
<td>L-NMMA</td>
<td>126.8±17.7</td>
<td>78.6±8.9</td>
</tr>
</tbody>
</table>

L-NMMA indicates A/ Q-monomethyl L-arginine. Values are mean±1 SEM expressed in nanograms angiotensin I per hour per milligram per 30 minutes incubation. *P<.05, †P<.005, basal vs L-NMMA.
TABLE 2. Influence of Calcium, W-7, and L-NMMA on Isoproterenol-Stimulated Renin Release

<table>
<thead>
<tr>
<th>Calcium Concentration</th>
<th>Basal Renin (ng Ang I/h)/mg</th>
<th>Isoproterenol-Stimulated (ng Ang I/h)/mg</th>
<th>Stimulated Less Basal (ng Ang I/h)/mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.6 mmol/L Ca²⁺ (n=11)</td>
<td>57.5±10.2</td>
<td>73.7±9.7</td>
<td>16.2±4.1*</td>
</tr>
<tr>
<td>2.6 mmol/L Ca²⁺+L-NMMA (n=6)</td>
<td>65.7±12.1</td>
<td>80.5±9.9</td>
<td>16.0±5.4*</td>
</tr>
<tr>
<td>2.6 mmol/L Ca²⁺+L-NMMA and W-7 (n=11)</td>
<td>63.4±8.3</td>
<td>98.7±10.3</td>
<td>35.1±6.4††</td>
</tr>
<tr>
<td>7.8 mmol/L Ca²⁺ (n=17)</td>
<td>37.8±5.4</td>
<td>63.9±9.1</td>
<td>26.1±8.1††</td>
</tr>
<tr>
<td>7.8 mmol/L Ca²⁺+L-NMMA and W-7 (n=6)</td>
<td>70.8±10.2</td>
<td>79.2±8.5</td>
<td>8.4±14.7</td>
</tr>
</tbody>
</table>

L-NMMA indicates N°-monomethyl L-arginine. Values are mean±1 SEM expressed in nanograms angiotensin I per hour per milligram per 30 minutes incubation.

*P<.05, †P<.001 vs stimulation by isoproterenol.
‡P<.025 vs change in controls.

Effect of Inhibition of Nitric Oxide Synthesis and Calmodulin on Renin Release

The influence of L-NMMA and calmodulin inhibition on renin release in high extracellular calcium is shown in Fig 2. In normal-calcium medium, renin release was 57.5±10.2 (ng Ang I/h)/mg per 30 minutes (n=11). Incubation in high-calcium medium suppressed basal renin release by 45% to 31.3±6.6 (ng Ang I/h)/mg per 30 minutes (n=11, P<.001 versus normal calcium). Incubation with L-NMMA in high-calcium medium resulted in a 55% increase in renin to 48.7±8.4 (ng Ang I/h)/mg per 30 minutes (P<.01 versus basal in high calcium). Incubation in high calcium with W-7 resulted in a further increase in renin release to 86.1±11.3 (ng Ang I/h)/mg per 30 minutes (n=6), which was not different from incubation with both L-NMMA and W-7 (70.8±10.2 [ng Ang I/h]/mg per 30 minutes [n=6]) or from basal release in normal-calcium medium. Thus, W-7 or the combination of L-NMMA and W-7 completely reversed the inhibition of renin by high extracellular calcium.

Although not presented, results similar to those with W-7 were obtained using the calmodulin inhibitor calmidazolium (5x10⁻⁵ mol/L, Calbiochem), suggesting that the reversal of calcium-mediated inhibition of renin release is through a calmodulin-mediated mechanism and is not drug specific.

Effect of Low Extracellular Calcium on Angiotensin II-Mediated Suppression of Renin Release

Angiotensin-dependent inhibition of renin release was found to be dependent on extracellular calcium. The addition of angiotensin to normal-calcium incubation medium resulted in a 45% decrease in renin release (52.9±9.5 versus 79.8±15.7 [ng Ang I/h]/mg per 30 minutes, n=12 per group). As before, incubation in low-calcium medium increased renin release by some 45% (116.6±13.7 [ng Ang I/h]/mg per 30 minutes, n=12) compared with normal medium. However, addition of angiotensin II to low-calcium medium had no additional effect on renin release (100.8±15.5 [ng Ang I/h]/mg per 30 minutes, n=11) but was significantly

Fig 1. Bar graph shows stimulation of renin release from renal cortical slices (compared with basal release, as percentage of basal) in media with different calcium concentrations induced by inhibiting nitric oxide synthesis with 10⁻⁴ mol/L N°-monomethyl L-arginine. *P<0.5, **P<.005 vs paired incubations in similar media.

Fig 2. Bar graph shows reversal of high-calcium medium-induced suppression of renin release from renal cortical slices by nitric oxide synthesis inhibition using 10⁻⁴ mol/L N°-monomethyl L-arginine (L-NMMA) or in combination with calmodulin inhibition using 5x10⁻⁵ mol/L, W-7. B refers to basal renin release in each medium. *P<.001 vs normal-calcium (2.6 mmol/L) medium; *P<.05 vs B in high-calcium medium. A1, angiotensin I.
higher than angiotensin II-suppressed renin in normal-calcium medium \( (P<.005) \).

**Effect of L-NAME on Angiotensin II–Mediated Suppression of Renin Release**

NO synthesis inhibition with L-NMMA completely reversed angiotensin II suppression of renin release. Angiotensin resulted in a 45% decrease in renin release (42.1±4.9 versus 76.7±10.6 \( \text{ng} \text{ Ang I/h/mg per 30 minutes} \), n=12 per group, \( P<.005 \)). Addition of L-NMMA to the medium tended to increase basal renin release and eliminated the angiotensin suppression of renin seen without L-NMMA (73.7±14.2 versus 89.7±10.0 \( \text{ng} \text{ Ang I/h/mg per 30 minutes} \), n=12 per group).

**Isoproterenol-Stimulated Renin Release, Nitric Oxide, and Calmodulin**

Isoproterenol stimulation of renin with L-NMMA and W-7 is shown in Table 2. Isoproterenol stimulated a 30% increase in renin release \( (P<.05) \). Addition of L-NMMA tended to increase basal renin release, but the response to isoproterenol was identical to that in the control medium. Addition of both L-NMMA and W-7 also tended to increase basal renin and potentiated isoproterenol-stimulated renin release by more than twofold \( (P<.025) \).

Incubation in high-calcium medium resulted in a 45% suppression of basal renin release. However, the response to isoproterenol was not inhibited and tended to be somewhat greater than in normal-calcium controls. As before, the addition of W-7 and L-NMMA reversed the inhibition of basal renin release. However, under these conditions isoproterenol could not stimulate renin release further.

**Discussion**

Our results suggest that at least part of the calcium-mediated inhibition of renin is by calcium-induced activation of afferent arteriolar endothelial NO that permeates the adjacent juxtaglomerular cells to inhibit renin release, presumably by the inhibitory second messenger cGMP \( .5,9,11 \).

The release of renin is the rate-limiting step in the formation of the potent vasoconstrictor angiotensin II. Renin is unusual in that its release is inhibited by increased intracellular calcium (reviewed in Reference 12). Most factors that inhibit renin release (in vitro) require extracellular calcium in the medium, including angiotensin, endothelin, vasopressin, ouabain, and the calcium ionophore A23187.12,13 Park et al13 have shown that renin is inhibited by calcium in a concentration-dependent manner, and even with normal extracellular calcium, there is a partial inhibition of basal renin release. They demonstrated that an intracellular concentration of \( 10^{-7} \) to \( 10^{-4} \text{ mol/L} \) calcium in a preparation of renal cortical slices was the threshold for inhibition. Calcium inhibition of renin is blocked by calcium channel antagonists, and calmodulin antagonists stimulate renin release, suggesting a calmodulin dependence.13

The present studies confirm the inverse relation between extracellular calcium concentration and renin release, as well as the potentiation of renin release by calmodulin inhibition from the in vitro preparation of renal cortical slices. Furthermore, these data also confirm that the angiotensin-mediated inhibition of renin is dependent on extracellular calcium. Although it has been proposed that intracellular calcium is an important inhibitory second messenger in the regulation of renin, the novelty of the present studies is the extent to which local synthesis of NO may be an important intermediate of this calcium-mediated inhibition.

NO is constitutively synthesized in the cytosol of the endothelial cells by a calcium-calmodulin–dependent process.1 The endothelial cell uses calcium as a transduction signal between a stimulatory signal and NO synthesis (reviewed in Reference 3). Well-characterized stimuli include bradykinin and acetylcholine. NO synthesis is stimulated by calcium in a concentration-dependent manner. Thus, the influx of extracellular calcium is an important component of agonist-induced NO synthesis, and this can be mimicked by the calcium ionophore A23187.2 The calcium influx is not mediated by voltage-dependent channels, is not inhibited by membrane depolarization, and is not mediated by sodium-calcium exchange. However, it is proposed to occur via some unspecified calcium channels.3

The present study confirms that the inverse relation between extracellular calcium concentration and renin release, but it also illustrates a direct relation between extracellular calcium and apparent NO synthesis. The reversal of calcium-mediated renin inhibition by the inhibition of NO synthesis with L-NMMA was amplified as the extracellular calcium was elevated. This potentiation of renin release by L-NMMA in normal-calcium medium has been previously reported.3 However, even with high-calcium medium, L-NMMA reversed the inhibition of renin by only 50% (compared with basal release in 2.6 \text{ mol/L} \text{ calcium medium}) whereas calmodulin inhibition completely reversed the inhibitory effect of high calcium. Thus, in the juxtaglomerular cells the second messenger role of calcium is to inhibit renin release, whereas in endothelial cells it is to stimulate NO synthesis, which in turn inhibits renin release in the adjacent juxtaglomerular cells through the formation of the inhibitory second messenger cGMP.

Marsden et al4 have studied glomerular endothelial cells and found them selectively responsive to certain agonists of calcium influx. They reported that bradykinin, ATP, thrombin, and platelet-activating factor increase endothelial intracellular calcium, whereas serotonin, acetylcholine, phenylephrine, endothelin-1, and angiotensin had no measurable effect. However, we have previously reported16 endothelium-dependent vasodilation to acetylcholine in the renal resistance vessels, suggesting that there may be different agonist affinity in different segments of renal vascular endothelium. Additionally, it has been reported that angiotensin (or its degradation products) may directly stimulate NO synthesis in vascular endothelium.18 The present study suggests that although angiotensin may not influence glomerular endothelial cells in culture, indirect evidence with angiotensin and NO synthesis inhibition suggests that most of the calcium-dependent, angiotensin-mediated inhibition of renin release from cortical slices is due to angiotensin-evoked NO synthesis. Because of the rapid breakdown of NO in situ, it seems most probable that this NO is from the endothelium of the afferent arteriole and permeates the adjacent juxtaglomerular cells to exert its effect. Despite an experimental design that induced similar degrees of renin...
inhibition by either increased extracellular calcium or addition of angiotensin, L-NMMA only partially reversed the effect of elevated-calcium-media but completely reversed the effect of angiotensin.

The inhibition of renin in vitro by cGMP or NO through formation of cGMP has been previously reported. The inhibition of renin by NO has been supported by studies in vivo in both the dog and rat.7 There is also convincing evidence that a significant and unique interaction between vasodilator NO and constrictor angiotensin is important in the regulation of renal blood flow.20-23 If NO buffers the constrictor influence of angiotensin in the kidney and inhibits the release of renin, it is intriguing to speculate that a selective angiotensin stimulation of NO synthesis in the renal resistance vessels might complete an integrative negative feedback loop between these important vasoactive factors. The present data support but do not directly confirm such a possibility.

It has been reported that cGMP is not only a renin inhibitory second messenger but also reverses cyclic AMP-mediated stimulation of renin by isoproterenol and arachidonic acid.9 It was therefore hypothesized that NO inhibition in normal- or high-calcium medium should not only elevate basal but potentiate isoproterenol-stimulated renin release. However, this was not the case. Although L-NMMA tended to increase basal renin release, it did not influence isoproterenol-stimulated renin release. This is similar to a previous study reporting that L-NMMA did not amplify isoproterenol-stimulated renin, although coinubcation with the L-arginine substrate for NO did inhibit the stimulatory response. It may be that hypercalcemia can inhibit adenylate cyclase and thus inhibit cyclic AMP formation, altering the response to isoproterenol. In the present study, inhibition of calmodulin remarkably potentiated the renin response to isoproterenol in normal-calcium but not high-calcium medium. The explanation for this response is not clear; but overall, these results do not suggest a cGMP-mediated inhibition of isoproterenol-stimulated renin under these conditions.

In summary, this study finds that extracellular media calcium inhibits renin release from renal cortical slices in a concentration-dependent manner. NO synthesis inhibition partially reverses this calcium-mediated effect, and calmodulin inhibition completely reverses it. This suggests that approximately half of the renin inhibition observed by increasing the extracellular calcium in vitro may be due to the subsequent stimulation of NO synthesis. Angiotensin inhibits basal renin release through a calcium-dependent pathway, and inhibition of NO synthesis completely reverses this effect. Angiotensin may be a particularly selective agonist for NO synthesis in the renal afferent arteriole, and this inhibitory pathway could be important in the "negative feedback" regulation of renin by angiotensin.

Acknowledgments

This work was supported by Grant-in-Aid HL-46683AO1 from the National Institutes of Health, Bethesda, Md. The author would like to acknowledge the significant contributions of Mrs D'Anna Potter, without whom this work could not have been completed.

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Hypertension. 1994;23:I40
doi: 10.1161/01.HYP.23.1_Suppl.I40

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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