Additive Effects of Aldosterone with Vasopressin or Angiotensin

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SUMMARY Rat tail arteries were incubated overnight in potassium (K)-free physiological saline solution (PSS) at 10°C, then returned to normal aerated PSS at 37°C for a 3-hour recovery period followed by standard chemical analysis. Cell sodium (Na) was measured following replacement of extracellular Na by lithium (Li) at 3°C. The addition of aldosterone at 10⁻⁷ M reduced free cell Na by about 3 mmol/kg dry weight (about 20%). Arginine vasopressin also lowered cell Na to the same degree. The minimal effective dose was about 25 pM (25 pg/ml, 0.01 mU/ml), and the maximal dose was about 250 pM. No effect was seen with higher doses (greater than 1.5 nM or 0.5 mU/ml). Tissues incubated in media containing 10⁻⁷ M aldosterone showed an exaggerated response to vasopressin evidenced by a near doubling of the maximum fall in cell Na produced by a tenfold smaller dose (25 pM). No significant change in cell K was observed while cell water tended to increase with lower doses. Angiotensin produced a similar reduction of cell Na at the same dose levels as vasopressin and was similarly additive with aldosterone. We suggest that these hormones enhance the transport of Na from luminal to basal sides of polarized cells and from cells to environment in symmetrical cells. (Hypertension 6: 242-248, 1984)

KEY WORDS • vascular smooth muscle • blood vessel • aldosterone • vasopressin • angiotensin • hypertension • vascular cations • sodium

RECENT studies have shown that enhanced sodium (Na⁺) transport is a characteristic feature of arteries in the spontaneously hypertensive rat (SHR) and in the rat with hypertension induced by deoxycorticosterone acetate (DOCA) or aldosterone.¹⁻³ This effect may involve a direct action of mineralocorticoids on the vascular smooth muscle cell since it can be reproduced by exposing the incubated rat tail artery to a low concentration of aldosterone in the range of 10⁻⁹ to 10⁻⁷ M for as little as 3 hours.⁴

Along seemingly separate lines, it has recently been reported that vasopressin stimulates Na⁺ transport in mouse fibroblasts in culture.⁵ This would be pertinent to the study of hypertension if vasopressin were to act similarly on the vascular smooth muscle cell. This seemed probable to us and especially interesting since some years ago we observed that small doses of vasopressin synergized with DOCA in accelerating the initial rise of blood pressure in the rat.⁶, ⁷ Interest in this fundamental problem has recently been rekindled by the work of Möhring et al.⁸ and followed by that of Crofton et al.,⁹ who have provided further evidence that the evolution of a steroid-induced hypertension depends on neurohypophysial activity.

Since the incubated rat tail artery has proven to be an appropriate preparation for demonstrating that aldosterone and DOCA stimulate net Na⁺ transport measured in terms of steady-state ion distribution, it was an obvious choice for our study of vasopressin. We added angiotensin to our study because of a recent report¹⁰ that it, too, stimulates Na⁺ transport in rat smooth muscle cells in culture. We report here that not only do these potent peptides stimulate net Na⁺ transport activity in vascular smooth muscle, but also that they do so in picomolar concentrations additively with aldosterone. These hormones that transfer Na⁺ and water from luminal to basal sides of polarized cells, as in the kidney, apparently produce analogous net transfers in the nonpolarized, symmetrical vascular smooth muscle between the interior of the cell and its environment.

Methods

Tail arteries were rapidly excised from adult male albino rats of an inbred Wistar strain anesthetized with pentobarbitone. They were halved, and each half placed separately into aerated (5% CO₂, 95% O₂) nor-
nal physiological salt solution (PSS) at 37°C for a 2-hour recovery period. Samples were then transferred to K-free physiological saline solution (PSS) for overnight incubation at 10°C to dissipate ionic gradients. On the next morning, the tissues were transferred to aerated PSS at 37°C for a 3-hour recovery period, after which extracellular Na was exchanged with lithium (Li) by washing the tissues for 45 or 90 minutes in cold Li-substituted PSS (LiPSS) at 3°C. They were blotted and transferred to weighing cups. Wet weights were obtained immediately; tissues were then dried to constant weight, defatted, extracted for 7 days in 4 ml of 0.75 N nitric acid, and ion contents determined by atomic absorption analysis. Detailed evidence concerning the accuracy and limits of this method has been presented elsewhere. 11, 12 Unless stated otherwise, groups of nine arteries were used throughout. All values are expressed in terms of kilograms of dry weight.

The composition of the basic PSS (expressed in mM) is: NaCl, 115.0; NaHCO₃, 25.0; NaH₂PO₄, 1.2; KCl, 5.0; CaCl₂, 1.7; MgSO₄, 1.2; and D-glucose, 11.0. D-aldosterone (Sigma Chemical Company, St. Louis, Missouri) was added to both the overnight K-free and the normal recovery media. Arginine-vasopressin (deamino-dicarba-arg-vasopressin, Beckman Instruments, Inc., Palo Alto, California) was made up fresh from stock containing 10 IU/ml prepared from powdered material containing 350 IU/mg. Angiotensin II (5-isoleucine form, Sigma) was similarly prepared from weighed stock. Doses are expressed as concentrations, pg/ml, which is almost the same as pM. Both peptides were added only to the normal PSS used during the recovery period.

Results

Effects of Vasopressin on Cell Sodium, Potassium, and Water

Vasopressin was added to the incubation medium used for the 3-hour recovery phase at 37°C at three dose levels: 25, 100, and 250 pg/ml. This covers the subpressor range of 0.01 to 0.1 mU/ml. The Na, K, and total tissue water (Vt) were measured directly. Extracellular water was measured as the volume into which the Li used for the final cold wash was distributed; cell water was measured as total less extracellular water. 4 The concentration of Na within the cell was derived from measured cell Na by subtracting a constant value for bound Na and by expressing the residual in terms of cell water. For this purpose, the operational constant was set at 10 mmol/kg dry wt. 13 The cell concentration of K was derived from measured tissue K by first subtracting extracellular K and then expressing the residual as if freely distributed in cell water. Because of the assumptions involved in these derivations, the values cannot be taken as absolute, but they are relatively sensitive indicators of change. The observations are shown in Table 1.

Vasopressin reduced total cell Na, as well as its concentration in free cell water. Although this effect was statistically significant only with the highest dose taken as a single point, all three points fell neatly and significantly in line when measured as regressions. Expressed as a percentage of change, Na fell 0.46% ± 0.03% (r² = 0.99.92) and [Na], fell 0.73% ± 0.01% (r² = 0.99.93) for every 10 pg/ml of vasopressin. No changes were observed in any other parameters.

A follow-up experiment was next designed to test the assumption that free cell Na was affected. Tissues were first partially depleted of Na by incubation in low-Na PSS (40 mM) in which NaCl was isosmotically replaced with sucrose for the 3-hour 37°C recovery phase. 13 They were then returned to normal PSS and the ensuing reentry of Na was followed. Nine groups of eight arteries each were used, the first to establish the steady-state reduced level of cell Na of tissues in 40 mM [Na], and the remaining eight groups for the determination of the reentry of Na 15, 30, 60, and 90 minutes after return either to normal PSS or to PSS containing 200 pg/ml vasopressin. The results are shown in Figure 1.

The reentry of Na was rapid and not significantly affected by vasopressin. The rate of reentry was not matched evenly by outward Na⁺ transport so that a significant overshoot of Na uptake was evident at 15 minutes. This was followed by the extrusion of sufficient Na to reestablish a new steady state at 30 minutes. More Na was extruded in the presence of vasopressin so that the average value for total cell Na in the three groups at steady state (n = 24) was significantly lower by almost 3 mmol/kg dry wt compared with controls. The corresponding values for cell water were similar in all groups at an overall average of 1.22 ±

<table>
<thead>
<tr>
<th>Group</th>
<th>Na (mmol)</th>
<th>K (mmol)</th>
<th>Vt (liters)</th>
<th>Vc (liters)</th>
<th>[Na] (mM)</th>
<th>[K] (mM)</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>25.3 ± 1.3</td>
<td>211 ± 6</td>
<td>3.29 ± 0.05</td>
<td>1.16 ± 0.03</td>
<td>13.0 ± 1.0</td>
<td>171 ± 4</td>
<td>9</td>
</tr>
<tr>
<td>Vasopressin 25 pg/ml</td>
<td>25 ± 1.9</td>
<td>216 ± 6</td>
<td>3.32 ± 0.04</td>
<td>1.19 ± 0.05</td>
<td>12.7 ± 1.5</td>
<td>173 ± 4</td>
<td>9</td>
</tr>
<tr>
<td>Vasopressin 100 pg/ml</td>
<td>24.4 ± 1.2</td>
<td>202 ± 4</td>
<td>3.35 ± 0.07</td>
<td>1.22 ± 0.06</td>
<td>12.0 ± 1.1</td>
<td>158 ± 7</td>
<td>9</td>
</tr>
<tr>
<td>Vasopressin 250 pg/ml</td>
<td>22.4 ± 0.5†</td>
<td>213 ± 3</td>
<td>3.37 ± 0.03</td>
<td>1.18 ± 0.03</td>
<td>10.6 ± 0.4*</td>
<td>171 ± 4</td>
<td>9</td>
</tr>
</tbody>
</table>

Vt = total tissue water; Vc = cell water.
* p < 0.05.
The increased Na gradient is also indicated by the fact that the controls required an increase of 9.2 mmol of gradient by about +5 mV. Pressin increased the Na

0.02 liters/kg dry wt. This yielded an average value for [Na] of 11.2 ± 0.5 mM in controls and 8.9 ± 0.4 mM in the treated groups. Thus, expressed as E\text{Na}, vasopressin increased the Na\textsuperscript{+} gradient by about +5 mV. The increased Na gradient is also indicated by the fact that the controls required an increase of 9.2 mmol of [Na]/kg dry wt. compared with 6.6 mmol in vasopressin-treated arteries to maintain the constancy of the [Na]/[Na\textsubscript{e}] ratio when [Na] was raised by 100 mM.

From this experiment we conclude that the reduced level of cell Na in vasopressin-treated arteries is due to enhanced net Na\textsuperscript{+} transport. In a parallel experiment, vasopressin at 100 pg/ml was without significant effect.

### Effects of Vasopressin Combined with Aldosterone on Sodium, Potassium, and Water

The effects of vasopressin on the transmembrane distribution of Na\textsuperscript{+} are evidently similar to those previously observed in arteries treated with aldosterone. Accordingly, the effects of adding vasopressin for 3 hours at 37°C to tissues continuously exposed to aldosterone following excision was explored next. The background level of aldosterone was maintained at 2.8 × 10\textsuperscript{-7} M, a level previously observed to be maximal.

Six doses of vasopressin were used with the highest dose at or close to a threshold pressor dose (1 mU/ml in our experience). The results are shown in Table 2.

As previously reported, aldosterone reduced the concentration of cell Na, in effect increasing the transmembrane concentration gradient. Vasopressin not only produced a further reduction in cell Na beyond that attributable to aldosterone, but did so with a dose tenfold smaller than when given alone. Thus, a maximal fall in [Na] of less than 3 mmol/kg dry wt produced by 250 pg/ml of vasopressin acting alone in the first experiment was here matched by the effect produced by 25 pg/ml in the presence of aldosterone. This effect was blunted at higher dose levels of vasopressin. No change in total cell K was observed, but a significant fall in cell water at higher vasopressin levels elevated cell K concentration.

The exchange of extracellular Na by Li during the final cold wash in cold LiPSS is usually associated with a negligibly small loss of cell Na in exchange for

![Table 2](image-url)
Li, but cannot safely be assumed to be so under experimental conditions. To check this, tissues were incubated either in PSS (control) or in PSS containing 2.8 x 10^{-7} M aldosterone with 250 pg/ml vasopressin (test), as in the preceding experiment, and washed for 45 or 90 minutes in cold LiPSS before final analysis. Groups of 12 arteries were used to establish each point. Although cell Na was reduced by aldosterone combined with vasopressin, as before, the rate of Na-Li exchange at 3°C was the same in treated arteries as in controls prepared either in PSS (control) or in PSS containing 2.8 x 10^{-7} M aldosterone were exposed to 200 pg/ml vasopressin for 15, 30, 60, or 120 minutes. As shown by the [Na] values in Table 3, the action of vasopressin was very rapid and substantially complete in the 15-minute samples. Again, collectively, the values for both Na and [Na] in the four groups of tissues exposed to vasopressin in the presence of aldosterone were significantly lower (p < 0.02) than in the comparable tissues exposed to aldosterone alone.

**Effects of Angiotensin Combined with Aldosterone on Sodium, Potassium, and Water**

The preceding observations suggested that angiotensin, like vasopressin, may interact with aldosterone. This was tested with six doses of angiotensin using tissues prepared as before in PSS containing 2.8 x 10^{-7} M aldosterone. The highest dose of angiotensin (5 ng/ml) is still subpressor in our experience. The results are shown in Table 4.

As with vasopressin, angiotensin also reduced both total and cell Na concentration beyond that produced by aldosterone alone. This was maximal with 100 pg/ml. No consistent change in cell K was observed. Cell water responded biphasically, increasing with lower doses and falling back again with higher levels.

**Synergism of Aldosterone with Vasopressin or Angiotensin**

Since both vasopressin and angiotensin reduce [Na], more than aldosterone alone, the question arises as to whether this is due to the simple addition of two mechanisms or the enhancement of related mechanisms. Enhancement was suggested in the previous experiments by both a lower threshold requirement and the attainment of a maximal response with a lower dose of agonist. This applies both to vasopressin and angiotensin.

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**Table 3. Cell Sodium and Water in Rat Tail Arteries after Sodium Enrichment and 3-hour Recovery in PSS at 37°C in the Continuous Presence of Aldosterone Followed by the Addition of Vasopressin for Various Times**

<table>
<thead>
<tr>
<th>Group</th>
<th>N(_i) (mmol)</th>
<th>V(_i) (liters)</th>
<th>[Na(_i)] (mM)</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSS alone</td>
<td>23 ± 0.4</td>
<td>1.22 ± 0.04</td>
<td>12.1 ± 0.9</td>
<td>8</td>
</tr>
<tr>
<td>PSS + aldosterone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 min</td>
<td>21.0 ± 0.4</td>
<td>1.17 ± 0.04</td>
<td>9.9 ± 0.4</td>
<td>8</td>
</tr>
<tr>
<td>30 min</td>
<td>20.5 ± 0.5</td>
<td>1.12 ± 0.05</td>
<td>9.6 ± 0.6</td>
<td>8</td>
</tr>
<tr>
<td>60 min</td>
<td>20 ± 0.3</td>
<td>1.23 ± 0.04</td>
<td>9.1 ± 0.7</td>
<td>8</td>
</tr>
<tr>
<td>120 min</td>
<td>21.7 ± 0.5</td>
<td>1.32 ± 0.02</td>
<td>8.9 ± 0.4</td>
<td>8</td>
</tr>
<tr>
<td>PSS + aldosterone +</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>200 pg/ml</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 min</td>
<td>19.6 ± 0.4</td>
<td>1.13 ± 0.02</td>
<td>8.4 ± 0.3</td>
<td>8</td>
</tr>
<tr>
<td>30 min</td>
<td>19.6 ± 0.4</td>
<td>1.20 ± 0.03</td>
<td>8.3 ± 0.7</td>
<td>8</td>
</tr>
<tr>
<td>60 min</td>
<td>20 ± 0.7</td>
<td>1.18 ± 0.04</td>
<td>8.8 ± 0.7</td>
<td>8</td>
</tr>
<tr>
<td>120 min</td>
<td>19.1 ± 0.6</td>
<td>1.20 ± 0.06</td>
<td>7.7 ± 0.6</td>
<td>8</td>
</tr>
</tbody>
</table>

*p < 0.02 vs PSS
†p < 0.02 vs aldosterone matched time.

**Table 4. Cell Sodium, Potassium, and Water in Rat Tail Arteries after Overnight Sodium Enrichment Followed by 3-hour Recovery in PSS at 37°C in the Presence of Aldosterone Combined with Angiotensin**

<table>
<thead>
<tr>
<th>Group</th>
<th>Na(_i) (mmol)</th>
<th>K(_i) (mmol)</th>
<th>V(_i) (liters)</th>
<th>V(_i) (liters)</th>
<th>[Na(_i)] (mM)</th>
<th>[K(_i)] (mM)</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (PSS)</td>
<td>22.8 ± 0.7</td>
<td>186 ± 4</td>
<td>3.16 ± 0.06</td>
<td>1.16 ± 0.04</td>
<td>11.2 ± 0.8</td>
<td>153 ± 5</td>
<td>9</td>
</tr>
<tr>
<td>Aldosterone 2.8 x 10^{-7} M</td>
<td>21.8 ± 0.7</td>
<td>203 ± 5</td>
<td>3.30 ± 0.08</td>
<td>1.24 ± 0.06</td>
<td>9.6 ± 0.7</td>
<td>157 ± 6</td>
<td>9</td>
</tr>
<tr>
<td>Aldosterone + angiotensin</td>
<td>20.4 ± 0.9</td>
<td>186 ± 4</td>
<td>3.29 ± 0.08</td>
<td>1.25 ± 0.04</td>
<td>8.3 ± 0.7</td>
<td>141 ± 5</td>
<td>9</td>
</tr>
<tr>
<td>10 pg/ml</td>
<td>20.4 ± 0.9</td>
<td>199 ± 4</td>
<td>3.24 ± 0.04</td>
<td>1.27 ± 0.02</td>
<td>8.4 ± 0.5</td>
<td>147 ± 4</td>
<td>9</td>
</tr>
<tr>
<td>50 pg/ml</td>
<td>19.7 ± 0.4</td>
<td>206 ± 5</td>
<td>3.27 ± 0.06</td>
<td>1.31 ± 0.03</td>
<td>7.4 ± 0.2*</td>
<td>149 ± 4</td>
<td>9</td>
</tr>
<tr>
<td>100 pg/ml</td>
<td>20.9 ± 0.8</td>
<td>205 ± 5</td>
<td>3.25 ± 0.07</td>
<td>1.37 ± 0.07</td>
<td>8.2 ± 0.7</td>
<td>144 ± 6</td>
<td>9</td>
</tr>
<tr>
<td>500 pg/ml</td>
<td>20.9 ± 0.8</td>
<td>196 ± 4</td>
<td>3.18 ± 0.07</td>
<td>1.21 ± 0.05</td>
<td>8.6 ± 0.5</td>
<td>154 ± 4</td>
<td>9</td>
</tr>
<tr>
<td>1 ng/ml</td>
<td>20.4 ± 0.6</td>
<td>196 ± 4</td>
<td>3.20 ± 0.05</td>
<td>1.21 ± 0.04</td>
<td>9.4 ± 0.7</td>
<td>154 ± 6</td>
<td>9</td>
</tr>
<tr>
<td>5 ng/ml</td>
<td>21.3 ± 0.7</td>
<td>195 ± 4</td>
<td>3.20 ± 0.05</td>
<td>1.21 ± 0.04</td>
<td>9.4 ± 0.7</td>
<td>154 ± 6</td>
<td>9</td>
</tr>
</tbody>
</table>

*p < 0.02 vs aldosterone.
The further testing of this interrelationship requires the direct comparison of dose-response curves. In the case of vasopressin, the problem was met by designing two experiments to be carried out on successive days with stringent attention to detail in the hope that they would prove to be comparable. In the first, a dose range of 25 to 500 pg/ml of vasopressin alone was examined; in the second, a similar range in the presence of 2.8 x 10^-7 M aldosterone. Judged by the near identity of control values, the two experiments were matched closely enough for direct comparison. The results are shown in Figures 2 and 3.

There was a distinct tendency for vasopressin at these levels to increase cell water. This amounted to about 6%, and although this was at the limit of detection, it was consistent and significant. With aldosterone as background, a similar increase was noted only with the lowest doses of vasopressin and appeared to reverse at higher levels. (A decrease of cell water at higher levels of vasopressin in the presence of aldosterone was also noted in the previous experiment).

As before, vasopressin decreased total cell Na, and this was augmented by vasopressin. The maximal response required > 200 pg/ml, and the threshold about 10 pg/ml. The additive effect was most apparent in the derived values for [Na]. Here the maximal reduction was equal to the sum of the agonists, but significantly smaller amounts of vasopressin were required to elicit both threshold and maximal effects.

For angiotensin, only a single experiment limited to four points, at 0, 25, 50, and 200 pg/ml in the presence or absence of aldosterone (2.8 x 10^-7 M), was used. As shown in Figure 4, this was sufficient to establish that angiotensin, like vasopressin, cooperated with aldosterone in reducing cell Na. This effect was again apparent in the derived values for [Na]. Thus, 200 pg/ml angiotensin alone reduced this from 11.8 ± 0.4 mM in controls to 9.9 ± 0.3 mM, a drop of 16%, and in the presence of aldosterone to 8.5 ± 0.6 mM, for a total drop of 28%.

Discussion
The attempt to resolve the functional interrelationship between the mineralocorticoid activity of the adrenal and the neurohypophysis has a venerable history. The complexity of the problem is illustrated by the fact that these at times appear to complement and at other
Figure 4. Arteries were prepared by overnight Na enrichment at 10°C in K-free PSS followed by a 3-hour recovery period at 37°C in normal PSS and a final wash in LiPSS at 3°C for 45 minutes. Clear bars indicate arteries incubated for the 3-hour recovery period in PSS containing various amounts of angiotensin. Shaded bars indicate arteries exposed to aldosterone in all incubation media. *p < 0.02 compared to controls of same bar color.

However, the mechanisms involved in the actions of vasopressin and angiotensin may be, they cooperated with but could not be identical with those used by aldosterone. First, the effects were evidently additive, and when combined, the increased steady-state Na⁺ gradient went beyond the maximum produced by aldosterone alone. Second, by the same index, arteries pretreated with aldosterone responded at a lower threshold dose to vasopressin or angiotensin, as indeed was the case for the pressor response to vasopressin in the intact rat. Finally, the response of Na⁺ transport to vasopressin was much more rapid than it was to aldosterone. Consequently, the effects were blunted at higher levels of vasopressin or angiotensin.

Some discussion of agonist levels is warranted. Although aldosterone enhanced net Na⁺ transport in the rat tail artery in vitro at 10⁻⁹ M, it produced its maximal effect at 10⁻⁷ M. The higher level was chosen for these experiments as the appropriate background for exploring the possibility of additive effects and separate mechanisms. Thus, while the data suggest that similar additive effects probably occurred at lower physiological levels of aldosterone, this question was not examined. Vasopressin used alone in vitro stimulated Na⁺ transport in the rat tail artery maximally at about 10⁻¹⁰ M, and in fibroblast cultures at about 10⁻¹² M. It has been observed in these experiments that when aldosterone was present, vasopressin was effective certainly at about 25 pM and probably at 10 pM, amounts similar to those observed in vivo where aldosterone was presumably also present. For angiotensin, amounts of the order of 10⁻¹⁰ M were required to stimulate Na⁺ transport in the incubated rat tail artery in vitro, as in vascular smooth muscle cells in culture.

Vasopressin and angiotensin did not exert the same actions in the picomolar as in the nanomolar range. Such a dose-dependent relationship was earlier observed in experiments concerning the pressor activity of angiotensin in the perfused rat tail artery and of vasopressin in the intact rat. Insofar as the pathogenesis of mineralocorticoid-dependent hypertension is concerned, it is clear now that the neurohypophysis may be involved without a substantial rise in circulating vasopressin, as was long ago suggested. Indeed, excessively high levels might well blunt the evolution of the hypertension. Evidently much remains to be reexplored with newer methods.

Finally, it should be noted that aldosterone, vasopressin, and angiotensin, which all stimulated net Na⁺ transport, were all potent pressor agents. Since they have all been shown to have stimulated protein synthesis, this alone may underlie their involvement in the sustained hypertensive process. We note, however, that recent observations appear to add catecholamines to the list of pressor agonists that also have stimulated Na⁺ transport. This leads us to consider seriously the possibility that blood pressure rose or fell as a direct function of Na⁺ transport.
References


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S M Friedman

Hypertension. 1984;6:242-248
doi: 10.1161/01.HYP.6.2.242

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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