Metoclopramide Stimulates Kaliuresis During Felodipine Without Affecting Its Natriuresis

Henk W. van Hamersvelt, Jack F.M. Wetzels, Robert A.P. Koene, Frans Th.M. Huysmans

Abstract Calcium entry blockers such as felodipine induce natriuresis without a parallel rise of potassium excretion. Previous studies with exogenous aldosterone and felodipine have suggested that the absence of kaliuresis might be explained by a felodipine-induced inhibition of aldosterone release. The natriuresis with calcium entry blockers could not be attributed to a similar mechanism but might be due to the stimulation of intrarenal natriuretic systems such as the dopaminergic system. We studied whether the selective dopamine antagonist metoclopramide prevents the natriuresis with low and therapeutic felodipine doses and whether metoclopramide-induced aldosterone release promotes kaliuresis with felodipine. Twelve healthy male volunteers participated in a randomized, placebo-controlled, crossover study comparing felodipine infusion during metoclopramide with felodipine alone. Metoclopramide had no significant influence on the pronounced and dose-dependent increases of renal plasma flow and urinary sodium excretion with felodipine. Metoclopramide increased plasma aldosterone concentration from 0.17±0.03 to 0.60±0.14 nmol/L, and subsequent felodipine infusion clearly increased urinary potassium excretion by 23±6 and 35±8 μmol/min (low and therapeutic doses, respectively). In contrast, potassium excretion remained stable with felodipine alone (+5±4 and +7±5 μmol/min, respectively). In conclusion, the natriuretic action of calcium entry blockers cannot be blocked by the selective dopamine antagonist metoclopramide. This natriuresis is accompanied by kaliuresis only in the presence of elevated endogenous aldosterone concentrations. The ability of calcium entry blockers to prevent a rise of plasma aldosterone thus seems essential for the prevention of urinary potassium losses. (Hypertension. 1994;24:633-639.)

Key Words • calcium channel blockers • felodipine • metoclopramide • aldosterone • natriuresis • kaliuresis

Calcium entry blockers (CEBs), especially dihydropyridines such as felodipine, are powerful vasodilating drugs useful for the treatment of hypertension.1 These drugs have short-term diuretic and natriuretic effects,2 which may contribute to their anti-hypertensive action. Clearance studies in humans3-6 and some micropuncture studies in animals7-9 have indicated that CEBs decrease proximal tubular sodium reabsorption. However, the mechanisms responsible for CEB-mediated natriuresis remain unknown. Since selective administration of a CEB into the renal artery stimulates natriuresis,10 an interaction with intrarenal natriuretic systems such as the dopaminergic system11 could be involved.

We and others have observed that the increased sodium excretion during calcium entry blockade is not accompanied by a parallel increase of potassium excretion.2,3,6,12 This is rather surprising in view of the aforementioned CEB-mediated decrease of proximal tubular sodium reabsorption. We have previously demonstrated that simultaneous administration of exogenous aldosterone and felodipine was followed by a large increase of kaliuresis.13 Therefore, the attenuation of potassium excretion during calcium entry blockade might be explained by the well-known CEB-mediated inhibition of aldosterone release.14

Dopamine exerts its biological effects through occupation of the type 1 and type 2 receptor subtypes (DA1 and DA2).15 Stimulation of DA1 receptors induces renal vasodilation and natriuresis,11,16 whereas activation of the DA2 receptors can promote sodium excretion indirectly by inhibition of norepinephrine and aldosterone release.11,17,18 DA1 receptor blockade attenuated the natriuretic effect of calcium entry blockade in spontaneously hypertensive rats,19 and preferential DA2 receptor blockade with metoclopramide prevented the natriuretic effect of a low dose of a CEB in hypertensive humans.20 Therefore, both DA1 and DA2 receptor stimulation should be considered as possible mechanisms mediating CEB-induced natriuresis.

Since selective DA1 receptor antagonists are not available for human studies, we also used metoclopramide to delineate the role of the dopaminergic system in the natriuretic effect of different felodipine doses. Metoclopramide also increases plasma aldosterone concentration (PAC)21 and thus enabled us to study the relation between CEB-induced natriuresis, endogenous aldosterone, and potassium excretion. In our previous study with exogenous aldosterone,22 this infusion resulted in a relatively high PAC above 2.5 nmol/L. We therefore questioned whether an increase of endogenous aldosterone within the normal physiological range would also increase potassium excretion during CEB-mediated natriuresis.

Methods

Subjects

Twelve healthy male volunteers participated in this study. All participants were free of medication. Ages ranged from 20 to 33 years (mean, 26); all had a blood pressure below 140/90 mm Hg (systolic, 102 to 140 mm Hg; diastolic, 66 to
were measured by standard semiautomated techniques, and PAH, inulin, sodium, potassium, and chloride concentrations of each urine collection period. In blood and urine samples, 0.66±0.05 mg in the last 90 minutes). Six additional 30-minute intervals were added: 0.08 μg/kg per minute for the last 60 minutes (cumulative dose, 0.25 μg/kg), 0.14 μg/kg per minute for another 30 minutes and 0.08 μg/kg per minute for the last 60 minutes (cumulative dose, 0.66±0.05 mg in the last 90 minutes). Each urine collection period, 600 mg lithium carbonate (16.2 mmol lithium) was given orally. Subjects were asked to refrain from smoking and the use of alcohol for the last 24 hours and from caffeine-containing beverages for the last 8 hours before clearance studies.

On study days, the subjects consumed a light breakfast and drank 375 mL tap water. One hour later, clearance experiments took place between 9 AM and 4 PM. On arrival, body weight was measured and water diuresis induced by an additional oral water load of 15 mL/kg body wt, resulting in a urinary osmolality of 79 mOsm/kg (48 to 122 mOsm/kg). During the entire experiment, 0.25% sodium chloride in 3.3% dextrose was infused at a rate of 400 mL/h to maintain diuresis and compensate for sodium losses observed previously during similar experiments with placebo.22 Urinary volume losses in excess of 400 mL/h were replaced orally by tap water. Subjects remained supine except for spontaneous voiding. With a continuous infusion technique described elsewhere,12 renal plasma flow (RPF) and glomerular filtration rate (GFR) were estimated by measurement of renal clearances of para-aminohippuric acid (PAH) and inulin (polyfructosan, Inutest, Laevosan-Gesellschaft), respectively. After 90 minutes of equilibration, two 30-minute baseline urine samples were collected. Thereafter, metoclopramide (Primperan, Delagrange) in 5% dextrose was infused at a rate of 20 mL/h for the first 30 minutes (1 mg metoclopramide/mL) or 5% dextrose alone was infused through a separate intravenous cannula into the upper arm at an infusion rate of 10 mL/h (10 mg metoclopramide/h) until the end of the experiment (cumulative dose, 45 mg metoclopramide in 240 minutes). During metoclopramide and dextrose, two 30-minute urine collections were made before felodipine or solvent was started in order to study the effect of pretreatment. Based on earlier studies,2 we used a felodipine infusion schedule aiming at stable, subtherapeutic plasma levels as measured just before felodipine or solvent was started. Infusion of felodipine alone was compared with placebo infusion and with felodipine during metoclopramide.

Statistics were performed with Statistical Analysis System (SAS) software, using the two-tailed Wilcoxon test for simple pairwise comparisons and repeated-measures ANOVA for comparison of baseline data. Probability values less than .05 were considered statistically significant. Results are presented as mean±SEM.

All 12 volunteers completed the three clearance experiments. The most common side effects were restlessness during or after metoclopramide infusion (6 of 12) and self-limiting headache during felodipine infusion (4 of 12 compared with 2 of 12 with solvent). One volunteer complained of drowsiness during felodipine infusion.

Baseline Data

Body weights and 24-hour urinary water, sodium, and potassium excretions were comparable before the three clearance experiments (Table 1). Baseline MAP was slightly lower before metoclopramide infusion (Fig 1). All other baseline levels of systemic and renal hemodynamics as well as baseline electrolyte excretions did not differ among the three experimental periods (Figs 1, 2; and Table 2).

Systemic and Renal Hemodynamics

Infusion of the low felodipine dose decreased MAP from a pretreatment level of 89±3 to 86±2 mm Hg (Fig 1) and increased heart rate from 55±2 to 60±2 beats per minute (bpm) (both P<.05 compared with changes with solvent). The therapeutic felodipine dose increased heart rate further to 65±3 bpm (P<.01), whereas the change in MAP no longer differed from the change with lithium was determined by atomic absorption spectrophotometry. In blood samples, hematocrit was determined by routine Coulter Counter, plasma renin activity (PRA) and PAC by radioimmunassay,24 and plasma felodipine levels by gas chromatography.26 Blood pressures and pulse rates were recorded at 3-minute intervals by an automatic device (Dinamap model 1846P, Critikon) that directly measures mean arterial pressure (MAP). The mean values of five consecutive readings in the middle of each urine collection period were used for analysis.

Of the various substances (x), clearances (Clx), urinary excretions (UX), and fractional excretions (FEx) were calculated according to standard formulas (U, representing the urinary concentration and V the urinary flow rate). Fractional filtration (FF) was calculated by GFR/RPF. GFR and RPF were adjusted to a standard body surface area of 1.73 m². Fractional proximal sodium reabsorption (FPNa) and fractional distal sodium reabsorption (FDNa) were calculated by the lithiun clearance method.25

FPRNa = 1-ClNa/GFR and FDNa = 1-ClNa/ClLi.

Results
TABLE 1. Steady-State Data Before Clearance Studies

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dext+Solv</th>
<th>Dext+Felo</th>
<th>Meto+Felo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, kg</td>
<td>73.1±1.5</td>
<td>72.9±1.6</td>
<td>72.9±1.6</td>
</tr>
<tr>
<td>Urine volume, mL/24 h</td>
<td>1315±83</td>
<td>1488±104</td>
<td>1424±134</td>
</tr>
<tr>
<td>Urinary sodium, mmol/24 h</td>
<td>135±10</td>
<td>139±9</td>
<td>156±20</td>
</tr>
<tr>
<td>Urinary potassium, mmol/24 h</td>
<td>75±5</td>
<td>77±7</td>
<td>80±8</td>
</tr>
</tbody>
</table>

Dext indicates dextrose; Solv, solvent; Felo, felodipine; and Meto, metoclopramide. Dextrose and solvent were both used as placebo. Values are mean±SEM.

solvent ($P>.10$, Fig 1). Metoclopramide pretreatment did not change blood pressure or heart rate and did not influence the felodipine-mediated blood pressure changes. During simultaneous infusion of metoclopramide and the therapeutic felodipine dose, the rise of heart rate was more pronounced than with felodipine alone (+16±3 and +10±1 bpm, respectively, $P<.05$).

Felodipine infusion alone induced dose-related increases of RPF (Fig 1) and decreases of FF (-0.023±0.004 at low dose and -0.037±0.005 at therapeutic dose; both $P<.05$ compared with solvent). Felodipine did not change GFR (Fig 1). Metoclopramide infusion had no major effect on renal hemodynamic parameters. Felodipine infusion induced the same renal vasodilation during metoclopramide as during dextrose, with comparable increases of RPF (low dose, +68±14 and +74±16 mL/min per 1.73 m²; therapeutic dose, +128±15 and +152±27 mL/min per 1.73 m², $P>.10$ for both doses; Fig 1).

**Diuresis and Natriuresis**

Felodipine infusion alone had distinct and dose-dependent diuretic and natriuretic effects, with parallel changes of chloride excretion (Fig 2 and Table 2). Metoclopramide induced a slight decrease of urinary flow rate and a minor decrease of sodium excretion that was only significant compared with dextrose preceding felodipine (Fig 2 and Table 2). During ongoing metoclopramide infusion, felodipine still induced pronounced increases of natriuresis and diuresis, which were comparable to the responses with felodipine alone (Fig 3). Only the increase of $U_{NaV}$ induced by the low felodipine dose tended to be attenuated by metoclopramide (+136±29 compared with +171±26 μmol/min with felodipine alone, $P=.06$).

Both felodipine doses significantly increased $C_{hi}$ (Table 2) and decreased calculated FPR$_{Na}$ (data not
TABLE 2. Electrolyte Excretions Before and During Drug and Placebo Infusions

<table>
<thead>
<tr>
<th>Variable</th>
<th>Period</th>
<th>Baseline</th>
<th>Pretreatment</th>
<th>Low-F</th>
<th>Ther-F</th>
</tr>
</thead>
<tbody>
<tr>
<td>UNaV, μmol/min</td>
<td>Dext+Solv</td>
<td>155±20</td>
<td>134±14</td>
<td>167±20†</td>
<td>175±19†</td>
</tr>
<tr>
<td></td>
<td>Dext+Felo</td>
<td>142±17</td>
<td>141±21</td>
<td>312±37</td>
<td>537±65</td>
</tr>
<tr>
<td></td>
<td>Meto+Felo</td>
<td>171±27</td>
<td>139±22*</td>
<td>275±38</td>
<td>489±81</td>
</tr>
<tr>
<td>UNaV, μmol/min</td>
<td>Dext+Solv</td>
<td>91±9</td>
<td>70±4†</td>
<td>58±4†</td>
<td>50±4†</td>
</tr>
<tr>
<td></td>
<td>Dext+Felo</td>
<td>70±8</td>
<td>63±7</td>
<td>68±8</td>
<td>70±7</td>
</tr>
<tr>
<td></td>
<td>Meto+Felo</td>
<td>84±11</td>
<td>66±9</td>
<td>88±12§</td>
<td>100±10‡</td>
</tr>
<tr>
<td>UC1V, μmol/min</td>
<td>Dext+Solv</td>
<td>129±18</td>
<td>100±11</td>
<td>226±24</td>
<td>423±54</td>
</tr>
<tr>
<td></td>
<td>Dext+Felo</td>
<td>115±16</td>
<td>98±14</td>
<td>239±35</td>
<td>430±71</td>
</tr>
<tr>
<td></td>
<td>Meto+Felo</td>
<td>143±23</td>
<td>114±16</td>
<td>332±50</td>
<td>457±65</td>
</tr>
<tr>
<td>Cly, mL/min</td>
<td>Dext+Solv</td>
<td>32±2</td>
<td>31±2</td>
<td>38±2</td>
<td>43±2</td>
</tr>
<tr>
<td></td>
<td>Dext+Felo</td>
<td>31±2</td>
<td>31±2</td>
<td>38±2</td>
<td>43±2</td>
</tr>
<tr>
<td></td>
<td>Meto+Felo</td>
<td>29±22</td>
<td>27±2†</td>
<td>36±3</td>
<td>44±4</td>
</tr>
</tbody>
</table>

*P<.01, †P<.05 compared with dext+felo for pretreatment effect, comparison of absolute changes from baseline level.
‡P<.01, §P<.05 compared with dext+felo for responses to felodipine infusion, absolute changes from pretreatment level.

Low-F indicates low felodipine dose; Ther-F, therapeutic felodipine dose; UNaV, UNaV, UC1V, urinary excretions of sodium, potassium, and chloride; Cly, lithium clearance; and definitions as in Table 1. Baseline values were comparable.

Kaliuresis

As observed in our other studies,6-13 potassium excretion steadily decreased with time on placebo days (Fig 4 and Table 2), which is probably related to the absence of oral potassium intake and the declining PAC in our supine subjects. In contrast, no such decrease of kaliure-

![Fig 3](image_url)

**Fig 3.** Bar graphs of absolute changes from pretreatment level of sodium excretion, potassium excretion, and distal sodium reabsorption illustrate responses to felodipine and solvent infusions. Left, Effect of low felodipine dose (Low-F); right, effect of therapeutic felodipine dose (Ther-F). *P<.05, **P<.01 compared with dextrose+felodipine.

![Fig 4](image_url)

**Fig 4.** Line graphs show plasma aldosterone concentration, potassium excretion, and distal sodium reabsorption during placebo and drug infusions. Infusion schedule is indicated by bars at the bottom. Open circles indicate dextrose followed by solvent; open squares, dextrose followed by felodipine; and closed squares, metoclopramide followed by felodipine. Low-F and ther-F indicate low and therapeutic felodipine doses. Absolute changes from baseline level were compared to evaluate pretreatment effect and absolute changes from pretreatment level to evaluate responses to felodipine infusion. *P<.05, **P<.01 for comparison of metoclopramide+felodipine and dextrose+felodipine; †P<.05, ‡P<.01 for comparison of dextrose+felodipine and dextrose+solvent.
Metoclopramide had no significant effect on potassium excretion, but the addition of felodipine to metoclopramide resulted in a prompt and clear-cut increase of kaliuresis (Table 2), with an increase of FEK from 0.13±0.02 to 0.18±0.02 at the low felodipine dose and 0.20±0.02 at the therapeutic felodipine dose (Fig 4). This pronounced kaliuretic response to felodipine during ongoing metoclopramide infusion was clearly different from the only modest response to felodipine alone (Fig 3).

**Hormones and Plasma Drug Levels**

PRA gradually decreased during combined placebo infusion from a baseline level of 0.66±0.13 to 0.46±0.14 nmol/L per hour at the end of the experiment. On the other two experimental days, similar decreases of PRA were observed without any significant influence of metoclopramide or of either felodipine dose. PRA decreased by 0.20±0.08 nmol/L per hour with felodipine alone and by 0.07±0.11 nmol/L per hour with felodipine during metoclopramide.

PAC also steadily decreased on placebo days and with felodipine alone (Fig 4). However, metoclopramide induced a large rise of PAC from 0.17±0.03 to 0.60±0.14 nmol/L (P<.01 compared with dextrose), and PAC remained clearly higher during subsequent felodipine infusion than during felodipine alone (low dose, 0.47±0.10 versus 0.12±0.02 nmol/L, P<.001; therapeutic dose, 0.32±0.08 versus 0.13±0.04 nmol/L, P=.02; Fig 4).

Infusion of the low felodipine dose led to stable, subtherapeutic plasma levels of approximately 4 nmol/L. Increasing the dose more than doubled the drug levels to a therapeutic level of 9 nmol/L (Fig 5). Felodipine plasma levels were slightly but significantly higher during concomitant metoclopramide infusion (low dose, 4.8±0.3 versus 3.9±0.3 nmol/L with felodipine alone; therapeutic dose, 9.3±0.4 versus 9.0±0.3 nmol/L; P<.05 for area under the curve).

**Discussion**

In the present study in healthy volunteers, the dopamine antagonist metoclopramide had no significant influence on the natriuretic and diuretic effects of either the low or therapeutic dose of felodipine. Only the natriuretic effect of the low felodipine dose was slightly but insignificantly attenuated by metoclopramide. Thus, our data suggest that the natriuretic and diuretic effects of calcium entry blockade cannot be explained by an interaction with the part of the intrarenal dopaminergic system that is blocked by metoclopramide.

Metoclopramide exhibits a preferential DA2 receptor selectivity; however, at high doses also tubular DA1 receptors are blocked. Thus, the question arises of whether the dose in our study was high enough to block the tubular DA1 receptors, which directly mediate dopamine-induced natriuresis. In two studies in healthy volunteers, the same metoclopramide infusion schedule as used in the present study inhibited the natriuretic responses to a low dose of dopamine and to the selective DA1 agonist fenoldopam. However, in another study, an infusion of approximately two thirds of our metoclopramide dose did not affect dopamine-mediated natriuresis in salt-loaded healthy subjects. These data might suggest that our metoclopramide dose was just high enough to block DA1 receptor-mediated natriuresis. However, the inhibitory effect of metoclopramide on sodium excretion in the aforementioned two studies might alternatively be ascribed to the observed and well-known metoclopramide-mediated release of PAC. Therefore, our results allow us to conclude only that DA1 receptors are not involved in the natriuretic effect of felodipine. These data thus confirm earlier studies in hypertensive patients, in whom the selective DA2 receptor antagonist domperidone did not influence the natriuretic effect of the CEB nicardipine.

Only the use of a potent DA1 receptor antagonist would have allowed us to draw definitive conclusions on the role of DA1 receptors in the natriuretic response to calcium entry blockade, but unfortunately such compounds are not available for human studies. Of note, the selective DA1 antagonist SCH 23990 prevented the natriuretic effect of nitrendipine and diltiazem in spontaneously hypertensive rats. However, it is difficult to translate these data to the human situation because very high drug doses were used, and consequently very large blood pressure changes were observed.

Our results do not exclude the possibility that metoclopramide slightly attenuates the natriuretic effect of low doses of CEBs. Although the effects of metoclopramide on felodipine-induced natriuresis failed to reach statistical significance, sodium excretion tended to be lower. However, plasma felodipine levels were higher during concomitant metoclopramide infusion, possibly because of a decreased metabolic clearance of felodipine. As the natriuretic effects of CEBs appear to be dose dependent, one might have expected higher sodium excretion rates in this period with higher felodipine levels. Our data are thus in line with observations in hypertensive patients, in whom metoclopramide largely prevented the natriuresis of a very low dose of nicardipine but did not affect the natriuretic action of a therapeutic dose. Taken together, these data might suggest a role, albeit limited, for the metoclopramide blockable part of the dopaminergic system in CEB-induced natriuresis. However, the attenuation of the natriuretic effect of low doses of CEBs could easily be explained by the metoclopramide-induced large increase of PAC, which might have attenuated the natriuresis with felodipine comparable to the attenuation of natriuresis in our study with exogenous aldosterone and felodipine. This possibility is further supported by the...
results of the present study in which metoclopramide attenuated the felodipine-mediated decrease of distal and not of proximal tubular sodium reabsorption.

In the setting of elevated PAC during metoclopramide infusion, felodipine induced an immediate increase of potassium excretion. This observation is noteworthy because we and others have observed that the natriuresis of calcium entry blockade is usually not accompanied by an increase of kaliuresis.5,6,12 This absence of kaliuresis is surprising in view of the fact that clearances studies in humans6,14 and some micropuncture studies in animals7,9 have indicated that CEBs decrease proximal tubular sodium reabsorption. Such a decrease in proximal sodium reabsorption and the subsequent increase of distal tubular sodium and fluid load should normally enhance potassium excretion, as is observed with diuretics such as furosemide.38 Thus, it seems likely that CEBs also act at a distal tubular site. In this respect, it is of interest that dihydropyridine CEBs can induce a rise of PRA without a parallel increase of PAC,2,14 possibly because of direct inhibition of aldosterone release by adrenal glomerulosa cells.39,40 We suggest that this inhibition of aldosterone release is essential for the dissociation between the natriuretic and kaliuretic effects of CEBs. In a previous study,12 we demonstrated that adding exogenous aldosterone to a felodipine infusion resulted in a major increase of potassium excretion that was more pronounced than with aldosterone alone. However, definite conclusions could not be drawn because PAC levels were not measured. Our present findings now confirm that elevated endogenous aldosterone levels within the physiological range, as induced by metoclopramide, also enabled felodipine to induce kaliuresis. In this respect, it should be noted that our study lacked a control period with metoclopramide alone. However, it is unlikely that metoclopramide administration per se is the cause of the increased potassium excretion, because other researchers have not observed such kaliuretic effects of metoclopramide.41-43

In conclusion, dopaminergic receptor blockade with metoclopramide does not prevent the natriuretic effect of low and therapeutic felodipine doses, thereby indicating that the metoclopramide blockable part of the dopaminergic system does not play a major role in the natriuretic action of CEBs. In contrast to felodipine alone, simultaneous infusion of metoclopramide and felodipine led to a marked kaliuresis as a consequence of the metoclopramide-mediated rise of aldosterone. This confirms earlier findings with exogenous aldosterone and indicates that CEBs will induce kaliuresis if sufficient amounts of aldosterone are available. The inhibitory effect of CEBs on aldosterone release thus prevents urinary potassium losses despite an increase of natriuresis and diuresis.

Acknowledgments

This work was supported by a grant (C86.617) from the Dutch Kidney Foundation and by Astra Pharmaceuticals BV, Rijswijk, Netherlands. Felodipine was supplied by AB Astra Hässel, Möln达尔, Sweden, where felodipine plasma levels also were determined. We thank Marijke Rodermond and Gertie van Casteren for their skillful technical assistance. We also would like to acknowledge the staff and coworkers of the laboratories of Clinical Chemistry (head: Dr Hans L. Willems) and the department of Experimental and Chemical Endocri-
Metoclopramide stimulates kaliuresis during felodipine without affecting its natriuresis.
H W van Hamersvelt, J F Wetzels, R A Koene and F T Huysmans

_Hypertension_. 1994;24:633-639
doi: 10.1161/01.HYP.24.5.633

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1994 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/24/5/633

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/