A Test of the “Epinephrine Hypothesis” in Humans

David S. Goldstein, Anna Golczynska, John Stuhlmuller, Courtney Holmes, Robert F. Rea, Ehud Grossman, Jacques Lenders

Abstract—According to the “epinephrine hypothesis,” circulating epinephrine taken up by sympathetic nerves is coreleased with norepinephrine during sympathetic stimulation and binding of coreleased epinephrine to presynaptic β-adrenoceptors augments exocytotic release of norepinephrine, contributing to high blood pressure. This study examined whether infusion of a physiologically active amount of epinephrine affects subsequent vascular responses and the estimated rate of entry of norepinephrine into regional venous plasma (norepinephrine spillover). Each of 3 experiments included intravenous infusion of 3H-norepinephrine, measurements of forearm vascular resistance, and intra-arterial infusion of epinephrine (3 ng/min per deciliter forearm volume). In experiment 1, subjects underwent lower body negative pressure (LBNP—25 mm Hg) before and after intra-arterial epinephrine; in experiment 2, LBNP and intra-arterial yohimbine before and after intra-arterial epinephrine; and in experiment 3, intravenous nitroprusside before and after intra-arterial epinephrine. In all subjects, intra-arterial epinephrine produced ipsilateral pallor and decreased forearm vascular resistance. Ipsilateral venous epinephrine increased by 10-fold. Epinephrine did not affect forearm vasoconstrictor responses to LBNP or vasodilator responses to intra-arterial yohimbine or intravenous nitroprusside; did not affect venous norepinephrine levels or norepinephrine spillover during LBNP, yohimbine, LBNP during yohimbine, or nitroprusside; and did not increase venous epinephrine levels during any of these manipulations. Loading of forearm sympathetic terminals with epinephrine therefore does not augment subsequent neurogenic vasoconstriction or norepinephrine release in the human forearm in response to sympathetic stimulation. The findings are inconsistent with the epinephrine hypothesis. (Hypertension. 1999;33:36-43.)

Key Words: epinephrine ▪ norepinephrine ▪ nervous system, sympathetic ▪ yohimbine ▪ nitroprusside

Several studies have reported that epinephrine can augment neurogenic vasoconstriction.1,2 Majewski and coworkers3,4 proposed a model to explain this. According to the “epinephrine hypothesis,” sympathetic nerve terminals take up circulating epinephrine by neuronal uptake (uptake-1); sympathetic stimulation coreleases epinephrine with norepinephrine, the sympathetic neurotransmitter; the coreleased epinephrine binds to β-adrenoceptors on sympathetic terminals; and binding of coreleased epinephrine to presynaptic β-adrenoceptors augments norepinephrine release during sympathetic stimulation.

The epinephrine hypothesis helps to explain how excessive adrenomedullary hormonal system activity can contribute to the development of essential hypertension by augmenting sympathoneural norepinephrine release.3–5 More generally, the hypothesis provides a mechanism whereby endogenous compounds taken up into nerve terminals can undergo corelease with the transmitter and prolong or exaggerate release of the transmitter by binding to facilitatory presynaptic receptors.

Previous studies about the epinephrine hypothesis in humans have led to different conclusions. Floras and coworkers1,6 reported that 30 minutes after brachial intra-arterial epinephrine infusion (50 ng/min), lower body negative pressure (LBNP) elicited a larger forearm vasoconstrictor response than before the epinephrine infusion, consistent with the epinephrine hypothesis. In contrast, Stein et al7 reported that intra-arterial epinephrine infusion at the same dose did not augment forearm norepinephrine spillover.

Previous studies did not assess whether epinephrine augments norepinephrine spillover responses to LBNP or to other stimuli that increase sympathoneural exocytosis. In the present study we hoped to obtain this information and test the epinephrine hypothesis more directly in 3 experiments. In each, epinephrine was infused intra-arterially into the brachial artery for a prolonged period (40 minutes) at a physiologically active dose to load sympathetic terminals. Regional vascular and neurochemical responses to manipulations expected to increase norepinephrine release were assessed before and after cessation of intra-arterial epinephrine. The
study used 2 systemic, 1 local, and a combination of systemic and local stimuli of sympathetically mediated exocytosis: LBNP,8 intravenous nitroprusside,9 intra-arterial yohimbine,10 and LBNP in the setting of intra-arterial yohimbine. By blocking presynaptic \( \alpha_2 \)-adrenoceptors, yohimbine augments norepinephrine release for a given amount of sympathetic traffic.10 3H-Norepinephrine was infused to distinguish norepinephrine spillover from clearance as determinants of plasma norepinephrine levels.

Methods

Subjects

Forty healthy, nonobese adult volunteers participated in this study after giving written informed consent. The protocol of the study was approved by the Intramural Research Board of the National Institute of Neurological Disorders and Stroke.

In all subjects, the medical history, physical examination, and routine laboratory tests (including complete blood count; serum glucose; renal, liver, and thyroid function tests; plasma cortisol; urinalysis; and ECG) showed no evidence of cardiovascular or any other diseases. None of the subjects took any medication for at least 2 weeks before the study. Subjects were instructed to refrain from smoking cigarettes or drinking alcohol or caffeine-containing beverages for at least 12 hours before the experiment.

Experimental Procedures

Epinephrine was given intra-arterially at a dose (3 ng/dL forearm volume per minute) that pilot studies demonstrated produced clear local vasomotor effects (hand pallor and decreased forearm vascular resistance [FVR]) without systemic hemodynamic changes.3H-Norepinephrine was given intravenously (1 \( \mu \)Ci/mL, 0.75 mL/min) to quantify norepinephrine spillover. Stimuli in each subject were repeated beginning 30 minutes after cessation of the 40-minute intra-arterial infusion of epinephrine.

Each experiment was performed in the morning in a quiet room at a temperature of 22°C to 23°C, with the subject supine. A brachial artery was cannulated for intra-arterial blood pressure monitoring and for local infusions and blood sampling. In the same arm, the antecubital vein was cannulated for blood sampling. The antecubital vein of the other arm was cannulated for systemic infusions. Forearm blood flow (FBF) was measured by strain-gauge, venous occlusion plethysmography (D.E. Hokanson) and expressed as milliliters of blood flow per deciliter forearm tissue per minute. Hand blood flow was excluded by a wrist cuff inflated to \( \sim \)100 mm Hg above systolic pressure. For each FBF determination at least 5 measurements were performed, and the results were averaged.

Experiment 1

This experiment was designed to determine effects of epinephrine loading of sympathetic terminals in the forearm on regional vasoconstrictor and norepinephrine spillover responses to sympathetic stimulation induced by LBNP. Each of the 8 subjects received \(^3\)H-norepinephrine intravenously for 20 minutes. FBF was measured and blood sampled from the artery and antecubital vein of the same arm (BL-1, Figure 1). With the \(^3\)H-norepinephrine infusion continuing, the subject underwent LBNP at \(-25\) mm Hg for 20 minutes. FBF was measured and blood sampled from the artery and antecubital vein of the same arm (LBNP-1). The intravenous infusion of \(^3\)H-norepinephrine was then stopped. Epinephrine was infused intra-arterially for 40 minutes. At the end of the epinephrine infusion, FBF was measured. Ten minutes later, an antecubital venous blood
Assays
The catechols in 1-mL aliquots of plasma were assayed by batch alumina extraction followed by high-pressure liquid chromatography with electrochemical detection.\textsuperscript{13} The limit of detection was \( \approx 5 \) pg/mL for each catechol.\textsuperscript{3} H-Norepinephrine in plasma and the infusate was measured in fractions of column effluent by liquid scintillation spectrometry.\textsuperscript{14}

Data Analysis
Forearm spillover of norepinephrine was calculated with the following equation\textsuperscript{15}:

\[
\text{Norepinephrine Spillover} = \frac{Q}{V} \left( \frac{A}{1 - E} \right)
\]

where \( Q \) is the regional plasma flow, \( V \) is the concentration of norepinephrine in regional venous plasma, \( A \) is the concentration of norepinephrine in arterial plasma, and \( E \) is the regional extraction fraction of \( ^3 \)H-norepinephrine.

Results
Forearm Blood Flow and Vascular Resistance
LBNP significantly decreased FBF and increased FVR, with or without concurrent intra-arterial yohimbine infusion, whereas intra-arterial epinephrine, intra-arterial yohimbine, and intravenous nitroprusside all decreased FVR (Figure 2). Infusion of epinephrine intra-arterially did not affect responses of FBF or of FVR to LBNP, LBNP in the setting of intra-arterial yohimbine, or intravenous nitroprusside.

Plasma Epinephrine
In all subjects, the arterial epinephrine concentration exceeded the venous epinephrine concentration (Figure 3). At the end of the intra-arterial infusion of epinephrine, the mean ipsilateral venous plasma epinephrine concentration averaged \( \approx 10 \) times the contralateral concentration (1.62\( \pm \)0.27 versus 0.16\( \pm \)0.08 nmol/L; \( n=4 \)). Across the 3 experiments, the mean values for arterial and venous epinephrine at BL-2 significantly exceeded those at BL-1 (\( t=3.02, t=2.87, t=2.87 \), 2-tailed \( P=0.007, P=0.007, P=0.005 \), respectively).

LBNP elicited relatively small, statistically nonsignificant increases in arterial and venous epinephrine concentrations, with similar epinephrine responses before and after intra-arterial epinephrine infusion, both with and without concurrent yohimbine administration. Nitroprusside increased epinephrine concentrations inconsistently. Venous plasma epinephrine concentrations during nitroprusside infusion were similar before and after intra-arterial epinephrine infusion.

Plasma Norepinephrine
Exposure to LBNP increased arterial and venous norepinephrine levels (\( t=6.47, t=3.67, t=3.67 \), \( P<0.001, P=0.008, P=0.008 \), respectively; Figure 4). Nitroprusside increased arterial and venous norepinephrine levels in all 7 of the 7 subjects who received it (\( P=0.008 \) by the nonparametric sign test). Yohimbine administration. Nitroprusside increased epinephrine concentrations inconsistently. Venous plasma epinephrine concentrations during nitroprusside infusion were similar before and after intra-arterial epinephrine infusion.

Plasma Norepinephrine
Exposure to LBNP increased arterial and venous norepinephrine levels (\( t=6.47, t=3.67, t=3.67 \), \( P<0.001, P=0.008, P=0.008 \), respectively; Figure 4). Nitroprusside increased arterial and venous norepinephrine levels in all 7 of the 7 subjects who received it (\( P=0.008 \) by the nonparametric sign test). Yohimbine administration. Nitroprusside increased epinephrine concentrations inconsistently. Venous plasma epinephrine concentrations during nitroprusside infusion were similar before and after intra-arterial epinephrine infusion.

Plasma Norepinephrine
Exposure to LBNP increased arterial and venous norepinephrine levels (\( t=6.47, t=3.67, t=3.67 \), \( P<0.001, P=0.008, P=0.008 \), respectively; Figure 4). Nitroprusside increased arterial and venous norepinephrine levels in all 7 of the 7 subjects who received it (\( P=0.008 \) by the nonparametric sign test). Yohimbine administration. Nitroprusside increased epinephrine concentrations inconsistently. Venous plasma epinephrine concentrations during nitroprusside infusion were similar before and after intra-arterial epinephrine infusion.

Plasma Norepinephrine
Exposure to LBNP increased arterial and venous norepinephrine levels (\( t=6.47, t=3.67, t=3.67 \), \( P<0.001, P=0.008, P=0.008 \), respectively; Figure 4). Nitroprusside increased arterial and venous norepinephrine levels in all 7 of the 7 subjects who received it (\( P=0.008 \) by the nonparametric sign test). Yohimbine administration. Nitroprusside increased epinephrine concentrations inconsistently. Venous plasma epinephrine concentrations during nitroprusside infusion were similar before and after intra-arterial epinephrine infusion.

Supplementary Experiment
Each of 7 subjects underwent intravenous nitroprusside infusion at increasing doses (0, 0.3, 0.65, and 1.3 \( \mu \)g/kg per minute), with measurements of total body and forearm norepinephrine spillover at each dose and, in 6 subjects, with peroneal skeletal sympathetic nerve traffic (muscle sympathetic nerve activity [MSNA]) measured simultaneously by microneurography.\textsuperscript{11,12}
After intra-arterial infusion of epinephrine, arterial and venous norepinephrine levels were similar to the corresponding levels before epinephrine infusion, at baseline, during LBNP, during yohimbine, during LBNP in the setting of yohimbine, and during nitroprusside.

**Forearm Norepinephrine Spillover**

Across the 3 experiments, forearm norepinephrine spillover at BL-2 averaged 23% higher than at BL-1 (t = 3.59, 2-tailed P = 0.002). Whereas LBNP increased arterial (“total body”) norepinephrine spillover significantly (t = 4.41, P = 0.003), LBNP failed to increase forearm norepinephrine spillover (Figure 5), regardless of epinephrine infusion.

Intra-arterial yohimbine increased forearm norepinephrine spillover similarly before and after intra-arterial epinephrine infusion. LBNP in the setting of yohimbine failed to increase forearm norepinephrine spillover before or after intra-arterial EPI infusion. Systemic infusion of nitroprusside increased forearm norepinephrine spillover substantially (t = 3.88, P = 0.008); however, intra-arterial epinephrine infusion did not enhance the nitroprusside-induced increment in forearm norepinephrine spillover.

**Supplementary Experiment**

Nitroprusside given intravenously produced dose-dependent increases in pulse rate (F = 30.2, P = 0.0001),
arterial plasma norepinephrine (F=14.3, P=0.0001), total body norepinephrine spillover (F=16.8, P=0.0001), and MSNA (F=4.2, P=0.03). Dose-related changes in mean arterial pressure, arterial plasma epinephrine, and forearm norepinephrine spillover were not statistically significant (Table). Intravenous nitroprusside at the highest dose elicited an ∼3-fold increase in MSNA but only an ∼60% increase in forearm norepinephrine spillover.

Discussion

Several studies have reported that administration of physiologically active amounts of epinephrine enhances neurogenic vasoconstrictor responses or enhances release of norepinephrine during sympathetic stimulation. The epinephrine hypothesis explains this as follows: Sympathetic nerve terminals take up circulating epinephrine; sympathetic stimulation coreleases the removed epinephrine with norepinephrine; the
coreleased epinephrine binds to β-adrenoceptors on sympathetic terminals; and the binding of coreleased epinephrine to the β-adrenoceptors augments further norepinephrine release, enhancing neurogenic vasoconstriction during sympathetic stimulation.

In the present experiments to test the epinephrine hypothesis, we used a physiologically active dose of intra-arterial epinephrine (3 ng/min per deciliter forearm volume), as indicated by pallor of the hand and by increased FBF in all subjects. The 40-minute infusion increased ipsilateral venous epinephrine levels by 10-fold without affecting contralateral venous epinephrine levels, indicating effective local concentrations without detectable increases in epinephrine levels in the systemic circulation.

The epinephrine hypothesis predicts that loading of local sympathetic terminals with epinephrine should enhance vasoconstrictor responses to subsequent sympathetic stimulation; however, intra-arterial epinephrine failed to augment subsequent vasoconstrictor responses to LBNP. Even in the setting of intra-arterial infusion of yohimbine, to block possible autoinhibition of norepinephrine release by α-2-adrenoceptors, epinephrine loading failed to augment LBNP-induced increases in FVR. Analogously, the epinephrine hypothesis predicts that during intravenous nitroprusside infusion, the extent of forearm vasodilation before epinephrine infusion should exceed that after epinephrine infusion because of enhanced reflexive release of norepinephrine from sympathetic terminals; however, the extent of nitroprusside-induced forearm vasodilation remained the same after as before intra-arterial epinephrine infusion.

Because of extraction of circulating epinephrine in passage through forearm tissues, arterial plasma epinephrine levels normally substantially exceed antecubital venous levels. According to the epinephrine hypothesis, after cessation of intra-arterial epinephrine infusion, epinephrine corelease with norepinephrine during sympathetic stimulation should decrease the magnitude of the arteriovenous decrement in plasma epinephrine levels. In all 3 experiments, however, the magnitude of the arteriovenous decrement in plasma epinephrine levels remained about the same after as before intra-arterial epinephrine infusion. The possibility remains that locally released epinephrine mainly undergoes extraneuronal uptake and metabolism before it can enter the venous drainage. A study in which intra-arterial infusion of 3H-epinephrine is used could test this.

Finally, and most importantly, the epinephrine hypothesis predicts that epinephrine loading of sympathetic terminals should enhance norepinephrine release during manipulations that increase exocytosis as a result of binding of coreleased epinephrine to stimulatory β-adrenoceptors on the terminals. In the present study, however, epinephrine loading did not augment arteriovenous increments in plasma norepinephrine levels or forearm norepinephrine spillover responses to LBNP, intra-arterial yohimbine, LBNP during intra-arterial yohimbine, or intravenous nitroprusside.

Because of extraction of circulating epinephrine in passage through forearm tissues, arterial plasma epinephrine levels normally substantially exceed antecubital venous levels. According to the epinephrine hypothesis, after cessation of intra-arterial epinephrine infusion, epinephrine corelease with norepinephrine during sympathetic stimulation should decrease the magnitude of the arteriovenous decrement in plasma epinephrine levels. In all 3 experiments, however, the magnitude of the arteriovenous decrement in plasma epinephrine levels remained about the same after as before intra-arterial epinephrine infusion. The possibility remains that locally released epinephrine mainly undergoes extraneuronal uptake and metabolism before it can enter the venous drainage. A study in which intra-arterial infusion of 3H-epinephrine is used could test this.

Finally, and most importantly, the epinephrine hypothesis predicts that epinephrine loading of sympathetic terminals should enhance norepinephrine release during manipulations that increase exocytosis as a result of binding of coreleased epinephrine to stimulatory β-adrenoceptors on the terminals. In the present study, however, epinephrine loading did not augment arteriovenous increments in plasma norepinephrine levels or forearm norepinephrine spillover responses to LBNP, intra-arterial yohimbine, LBNP during intra-arterial yohimbine, or intravenous nitroprusside.

Inadequate numbers of subjects in the 3 experiments probably do not explain the negative results. For instance, in experiment 3, when we considered forearm norepinephrine spillover as the dependent measure, at a significance level (α) of 0.05, 7 subjects, a population standard deviation (σ) of 1.0 pmol/min per deciliter, and a sought response to nitroprusside after intra-arterial epinephrine administration 50% larger than the response to nitroprusside before epinephrine administration (δ, 4.2 pmol/min per deciliter), ϕ = δ/σ = 4.2, the power would exceed 0.95 by far.16

LBNP reflexivity decreases FBF, and forearm norepinephrine spillover depends to some extent on regional blood flow.15 Thus, the failure to increase forearm norepinephrine spillover during LBNP could have resulted from combined

---

**Figure 5.** Mean values (± SEM) for the estimated rate of entry (spillover [SO]) of norepinephrine (NE) in the forearm (FA). The same experiments as in Figure 2 were performed. Other abbreviations are as in Figure 2 legend.
influences of vasoconstriction, which would have decreased norepinephrine spillover, and increased exocytotic release of norepinephrine, which would have increased norepinephrine spillover. The flow dependence of norepinephrine spillover has led investigators to devise a flow-independent index of norepinephrine release into the extravascular space (extravascular appearance rate [EAR]), on the basis of the formula: EAR = Norepinephrine Spillover/(1 – E), where E is the regional extraction fraction of 3H-norepinephrine. When we apply the formula to the data in the present study, intravenous nitroprusside increased forearm EAR from 4.9 ± 0.6 pmol/min per deciliter, or 5-fold, before epinephrine loading and from 4.2 ± 0.8 to 10.6 ± 3.2 pmol/min per deciliter after epinephrine loading, indicating no epinephrine-related enhancement of norepinephrine release into the extravascular space. When we apply the same formula to the data in experiment 1, intravenous nitroprusside increased forearm EAR from 4.9 ± 2.0 to 19.6 ± 10 pmol/min per deciliter, or ≈5-fold, before epinephrine loading and from 4.2 ± 0.8 to 10.6 ± 3.2 pmol/min per deciliter after epinephrine loading. Thus, on correction for flow dependence of norepinephrine spillover, LBNP did not increase the responses of EAR to stimuli that increase exocytosis. The potentially confounding effects of decreased blood flow also would not explain the present finding of a larger proportional increase in peroneal MSNA than in the forearm norepinephrine spillover during intravenous nitroprusside infusion, since nitroprusside increases FBF.

Consistent with the epinephrine hypothesis, Floras and coworkers reported that after intra-arterial infusion of epinephrine, LBNP elicited a larger forearm vasoconstrictor response than before the infusion. In contrast, Stein et al used intra-arterial infusion of isoproterenol to stimulate forearm norepinephrine spillover and observed no delayed facilitatory effects of intra-arterial isoproterenol in either normotensive or borderline hypertensive subjects. Thompson et al reported that intravenous epinephrine did not augment cardiac norepinephrine spillover in humans. Adrenalectomized humans have normal vascular and plasma norepinephrine responses to various stimuli, which also argues against a modulatory role of circulating epinephrine in neurogenic vasoconstriction. Preclinical studies designed to test the epinephrine hypothesis comprehensively have also failed to confirm it.

The basis for the absence, in the present study, of LBNP-induced increases in values for indices of local norepinephrine release, despite consistent LBNP-induced sympathoneural stimulation and forearm vasoconstriction, remains obscure. Others have noted relatively small increases in forearm norepinephrine spillover during LBNP at −15 mm Hg. Analogously, in the present study, nitroprusside-induced proportional increases in directly recorded MSNA exceeded those in forearm norepinephrine spillover. Most of 3H-norepinephrine entering the forearm undergoes removal by nonneuronal cells, whereas most of endogenously released norepinephrine undergoes removal by neuronal uptake. Perhaps in the forearm, assumptions about mixing of endogenous and 3H-norepinephrine may not apply.

Total body norepinephrine spillover and arterial and venous plasma epinephrine levels all were higher 30 minutes after cessation of intra-arterial epinephrine infusion than before the infusion. A small amount of epinephrine could have remained in the stopcock apparatus after the intra-arterial infusion; however, this seems unlikely, because fluid lacking epinephrine was infused continuously via the same apparatus during the 30 minutes after cessation of intra-arterial epinephrine infusion. Retention of epinephrine in the stopcock would also not explain the higher value for total body norepinephrine spillover after than before intra-arterial epinephrine. Stein et al also reported higher total body norepinephrine spillover after than before intra-arterial epinephrine. They speculated that the increase in total body norepinephrine spillover after intra-arterial epinephrine could have resulted from effects outside the forearm of epinephrine that had entered the systemic circulation. The present results cast doubt on this explanation, because whereas intra-arterial epinephrine infusion increased venous epinephrine ipsilaterally by 10-fold, the infusion did not increase venous epinephrine contralaterally at all; in other words, little if any of the locally infused epinephrine entered the systemic circulation. Persson et al reported that after cessation of systemic epinephrine infusion, elevated MSNA and plasma norepinephrine persisted, by mechanisms that were obscure. Thus, 3 studies by different groups have obtained evidence for sus-
tained stimulatory effects of infused epinephrine on sympathetic outflows. A possibility is that intra-arterial epinephrine somehow altersafferentinformation to the central nervous system, increasing sympathoneural and adrenomedullary outflows. One could test this by measuring MSNA after brachial intra-arterial infusion of epinephrine. In the present study, this was done successfully in 5 subjects, and in 4 of the 5, MSNA was higher at BL-2 than at BL-1; however, the mean increase (15%) was not statistically significant, and when the low number of subjects is considered, the data are inconclusive.

In summary, because epinephrine loading failed to augment responses of FVR, regional venous epinephrine levels, or indices of norepinephrine release during exposure to stimuli that increase sympathetically mediated exocytosis, the present findings are inconsistent with the epinephrine hypothesis in humans.

References
A Test of the "Epinephrine Hypothesis" in Humans
David S. Goldstein, Anna Golczynska, John Stuhlmüller, Courtney Holmes, Robert F. Rea, Ehud Grossman and Jacques Lenders

Hypertension. 1999;33:36-43
doi: 10.1161/01.HYP.33.1.36

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1999 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/33/1/36

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/