Urinary Potassium Excretion and Sodium Sensitivity in Blacks

Abraham Aviv, Norman K. Hollenberg, Alan Weder

Abstract—Based on racial differences in urinary potassium excretion and responses to diuretics, we present a model suggesting that a major cause of sodium sensitivity in blacks is an augmented activity of the Na-K-2Cl cotransport in the thick ascending limb of Henlé’s loop. This would result in an increased ability to conserve not only sodium but also water, and an upward and rightward shift in the operating point of tubuloglomerular feedback, which may cause an increase in the glomerular capillary hydraulic pressure and predilection to glomerular injury with and without hypertension. In this sense, the biological implication of sodium sensitivity in blacks and in humans in general has ramifications above and beyond salt-evoked increase in blood pressure. (Hypertension. 2004;43:1-7.)

Key Words: blacks ■ hypertension, essential ■ kidney ■ potassium ■ sodium

Blood pressure of a subset of the human population rises as a result of an increase in the intake of salt (sodium chloride). Individuals who manifest this trait are salt sensitive. As sodium (and chloride) balance must be preserved to sustain life, salt-sensitive and salt-resistant subjects maintain sodium balance. What distinguishes salt-sensitive from salt-resistant subjects is that in the face of a high-salt intake, salt-sensitive subjects raise their blood pressure, ultimately maintaining sodium balance by resorting to pressure natriuresis. However, a habitually high salt consumption in susceptible individuals may exert biological effects other than salt-evoked blood pressure elevation, including left ventricular hypertrophy, stiffness of conduit arteries, and stroke.

The kidneys are the main player in salt sensitivity, but mechanisms causing this trait are a matter of conjecture. Lessons from rare, monogenic forms of hypertension and hypotension arising from abnormalities in renal sodium handling suggest that salt sensitivity need not be a single entity; rather, it is probably a clinical manifestation of a number of renal disorders that result in altered electrolyte homeostasis and thus blood pressure elevation.

Salt sensitivity in blacks has begged for a physiological explanation ever since the predilection of this group to essential hypertension and progressive renal damage has come to light. In a previous communication, we offered a paradigm that explains salt sensitivity in blacks. This article further expands the model by proposing that the differences in renal potassium handling between blacks and whites reflect ethnic variation in the fractional reabsorption of sodium in specific renal tubular segments. Moreover, we propose that mechanisms in the renal regulation of sodium may explain the predisposition of blacks to sodium-induced elevation of blood pressure and also to sodium-induced glomerular damage. Here, we refer to salt sensitivity as “sodium sensitivity,” albeit some research has suggested that not only sodium but also chloride, potassium, and perhaps other nutrients may contribute to the salt-sensitivity trait.

Although irrefutable evidence for a specific intrinsic renal process causing sodium sensitivity in blacks, and for that matter in the general population, does not exist, we have taken advantage of recent insights into the renal handling of sodium and potassium to reinterpret data generated as far back as a generation ago. We emphasize in this regard that although as a group blacks have increased propensity to sodium sensitivity, this trait is observed in other ethnic groups.

Clinical Observations Supporting the Sodium Sensitivity Model in Blacks

Our model of sodium sensitivity in blacks is based on a series of clinical observations. Compared with whites, blacks have lower plasma renin activity (PRA) and greater reduction in blood pressure in response to thiazide diuretics. With high-sodium intake, compared with whites, blacks have a greater glomerular filtration rate (GFR)/renal plasma flow (RPF) ratio (the filtration fraction) caused either by a relatively higher GFR or by a lower RPF. With a lower RPF, they have a greater increase in RPF (without a change in the GFR) in response to angiotensin-converting enzyme (ACE) inhibition. With low-sodium intake, the GFR/RPF in blacks is not different from that of whites. Further, ACE inhibition is more effective than other antihypertensive agents in attenuating hypertension.

Received September 19, 2003; first decision November 21, 2003; revision accepted January 22, 2004.
From the Hypertension Research Center (A.A.), Cardiovascular Research Institute University of Medicine and Dentistry of New Jersey, New Jersey Medical School, Newark; Departments of Medicine and Radiology (N.K.H.), Brigham and Women’s Hospital, Harvard Medical School, Boston, Mass; and Division of Hypertension (A.W.), Department of Internal Medicine, University of Michigan, Ann Arbor.
Correspondence to Abraham Aviv, Room F-464, MSB Hypertension Research Center, Cardiovascular Research Institute, University of Medicine & Dentistry of New Jersey, New Jersey Medical School, 185 South Orange Avenue, Newark, NJ 07103. E-mail avivab@umdnj.edu

Hypertension is available at http://www.hypertensionaha.org

DOI: 10.1161/01.HYP.0000120155.48024.6f
ating the progressive decline in kidney function of blacks who manifest kidney disease with essential hypertension. The physiological mechanism linking these observations may be tubuloglomerular feedback (TGF).

Resetting the TGF operating point upward and rightward shifts the balance of vascular tone between the afferent and efferent arterioles, so that the afferent arterioles are relatively vasodilated or the efferent arterioles are relatively vasoconstricted. This scenario is consistent with observations that with high-sodium intake, the GFR/RPF is higher in blacks than in whites. Low-sodium intake or treatment with ACE inhibitors abolishes differences between blacks and whites. In addition, the finding that ACE inhibition increases RPF more in blacks than in whites, without changing GFR, suggests that ultimately, ACE inhibition exerts its effect by vasodilating efferent arterioles more than afferent arterioles, thereby restoring the balance in vascular tone between these vessels in blacks.

Conventionally, glomerular hyperfiltration (high GFR) is referred to as an absolute elevation of GFR. In the context of our model, we consider glomerular hyperfiltration to result from circumstances when the afferent arterioles are relatively more dilated (or the efferent arterioles are relatively more constricted) than they should be to maintain the appropriate GFR for a given RPF, regardless of whether absolute GFR is reduced, normal, or increased.

The idea that sodium sensitivity entails a higher GFR/RPF has been proposed with respect to blacks and others. What is novel about our model is that it explains this phenomenon based on an upward and rightward shift in the TGF operating point. Moreover, the tradeoff for a shift in the TGF operating point is an increase in glomerular capillary hydraulic pressure, which can ultimately lead to glomerular damage. Such a possibility raises questions of causality: does hypertension in blacks always precede renal damage? Can sodium-evoked renal injury be the cause rather than the result of hypertension in a subset of blacks?

Dysfunctional Tubular Sodium Reabsorption and Salt Sensitivity: What Counts Is not the Amount but the Location
To maintain sodium balance, the kidneys must reabsorb most of the filtered sodium and excrete excess sodium, but our model suggests that what matters with respect to sodium sensitivity is where the sodium is being reabsorbed disproportionately. The lower PRA in blacks suggests that their predilection to sodium sensitivity could arise from: (1) a primary increase in sodium reabsorption downstream to the proximal tubules with or, as discussed, even without expansion of the extracellular volume (ECV); (2) a primary increase in proximal tubular sodium reabsorption resulting in the expansion of the extracellular fluid volume (ECFV); and (3) a primary reduction in sodium reabsorption by the proximal tubules, leading to tubular hyperperfusion of the macula densa and suppression of renin release without expansion of the ECV. Are there then any clues as to which sodium transport site is involved in sodium sensitivity in blacks? We propose that differences between blacks and whites in the urinary excretion of potassium and in the responses to diuretics provide crucial tip-offs.

Urinary Potassium Excretion in Blacks
Blacks have been consistently observed to excrete less potassium in their urine than do whites. Total urinary potassium excretion largely reflects potassium intake, but the difference in urinary potassium excretion between blacks and whites may not only result from a universally lower intake of potassium in blacks.

Three studies documented renal potassium excretion in blacks and whites not only under basal conditions but also after potassium supplementation in the form of potassium chloride. Voors et al supplemented their subjects with 80 mmol/d potassium for 4 days, Wong et al supplemented their subjects with 20 mmol/d potassium for 1 week, and Langford et al supplemented their subjects with 80 mmol/d potassium for 10 weeks. In all 3 studies, daily urinary potassium excretion was lower in blacks than in whites with and without potassium supplementation. Langford and Voors concluded that because blacks could raise their urinary potassium excretion with potassium supplementation, low urinary potassium excretion probably resulted from habitually low-potassium intake in blacks. What their findings actually showed, however, was that urinary excretion of potassium was lower in blacks than in whites, even when both groups were potassium-supplemented. Further support is derived from the study of Luft et al, who examined blacks and whites in a metabolic unit of a clinical research center for 15 days. All subjects were maintained on the same diet (potassium intake at 80 mmol/d with different regimens of sodium-loading, reaching as high as 1500 mmol/d). Blacks consistently excreted less urinary potassium than did whites. By the end of the study, whites had a net potassium deficit of −334 mmol, whereas blacks had a net potassium deficit of only −45 mmol. It is difficult to reconcile such observations with the idea that the lower urinary potassium excretion in blacks is caused by a chronic systemic deficit in potassium, particularly in light of a recent study showing that the total body potassium, primarily reflecting muscle mass, is actually higher in blacks than in whites until the ninth decade of life.

If racial differences in urinary potassium excretion were solely related to a lower potassium intake in blacks, then manipulation of dietary sodium intake would be unlikely to influence the racial differences in urinary potassium excretion. However, Price et al showed that with a diet producing high urinary sodium (200 mmol Na, 100 mmol K per day), the daily excretion of potassium in blacks was 55 mmol compared with 70 mmol in whites. With a low-sodium intake (10 mmol Na and 100 mmol K per day), the daily urinary potassium excretion was, respectively, 73 and 71 mmol in the same blacks and whites. Interestingly, intake of potassium in the form of potassium bicarbonate was associated with prevention of salt-evoked blood pressure elevation and comparable urinary excretion of potassium in blacks and whites, suggesting that chloride availability is a factor in the lower urinary excretion of potassium in blacks.

To maintain potassium balance, potassium excretion via other routes must be higher in blacks than in whites. There is
no evidence that sweat potassium losses differ between the 2 racial groups, although detailed research specifically addressing this question has not been performed. Examination of urine and fecal potassium in 10 black and 11 white South Africans revealed a urinary potassium excretion of 38.2 and 78.3 mmol for whites and blacks, respectively. The 24-hour fecal excretion of the ion was 15.0 and 20.8 mmol for blacks and whites, respectively. The total 24-hour excretion of potassium via the urine and feces was indeed lower in blacks (53.2 mmol) than in whites (99.1 mmol), indicating a lower intake of potassium in South African blacks. However, the ratio between fecal and urinary potassium was considerably higher in blacks (0.39) than in whites (0.26) in this small cohort. Thus, for a given potassium intake, black South Africans excreted a greater proportion of potassium via the gastrointestinal tract than did whites. Similarly, we have found in a cohort comprising only whites that on a fixed oral potassium intake, the fecal excretion of potassium was inversely correlated with the urinary excretion of the ion (unpublished data). Based on these findings, we suggest that as per black South Africans, the fecal urinary potassium excretion is higher in blacks than in whites, possibly via potassium excretory mechanisms in the colon.

**Further Clues for Sodium Sensitivity in Blacks Based on Potassium Excretion in Response to Diuretics**

Potassium transport is tightly linked to sodium reabsorption in the distal tubules and cortical collecting ducts. Which sodium transport mechanisms might explain the lower urinary excretion of potassium in blacks? The focus here is on 3 sodium transport systems that operate downstream to the proximal tubule. They are the amiloride-sensitive, epithelial sodium channel (ENaC), the thiazide-sensitive, sodium-chloride cotransport (Na-Cl cotransport), and sodium-potassium-chloride cotransport (Na-K-2Cl cotransport), which is sensitive to loop diuretics such as furosemide or bumetanide.

The bulk of potassium excreted in the urine gains access to the distal tubules and collecting duct because the transepithelial electrical potential is negative on the luminal side. This electrical potential is primarily generated by the ENaC, a transport system that is highly responsive to aldosterone. It consists of an increase in the abundance of the α subunit of the ENaC and a shift in the distribution of all 3 subunits of the ENaC (α, β, γ) from the cytoplasm to the apical membrane. Therefore, aldosterone is a major regulator of potassium excretion via the ENaC. We note in this regard that potassium excretion exhibits diurnal pattern and that in humans, the peak excretion is approximately mid-day, a phenomenon that is only slightly dependent on aldosterone level but is correlated with bicarbonaturia.

The hallmark of disorders that cause an increase in the activity of the ENaC is an increase in the urinary excretion of potassium. Because blacks excrete less potassium in the urine than do whites, it is unlikely that sodium sensitivity in blacks is the result of an increase in the activity of the ENaC. A recent study by Pratt et al showed that treatment with amiloride for 1 week caused a reduction in blood pressure in whites but a paradoxical increase in the blood pressure in blacks. Treatment with amiloride during this short time period reduced urinary potassium, with whites showing twice the reduction in potassium excretion as did blacks, although this ethnic difference was not statistically significant. Thus, there is no evidence for an increase in ENaC activity in blacks compared with whites in the distal tubules and collecting ducts. If anything, Pratt’s data suggest that the activity of the ENaC may be lower in blacks than in whites.

It is unlikely that the lower urinary potassium excretion in blacks is caused by low circulating aldosterone, because potassium supplementation abolished differences in serum aldosterone between blacks and whites but not the gap in the urinary potassium excretion. In addition, direct mineralocorticoid stimulation (ie, treatment with fludrocortisone) failed to close the gap in urinary potassium excretion between blacks and whites. In another study in a metabolic ward, baseline aldosterone levels were not different between blacks and whites, yet urinary potassium excretion was considerably lower in blacks.

**Tubular flow rate** is another important determinant of potassium excretion. An increase in tubular flow rate, for example, caused by an increase in sodium delivery to distal nephron segments and cortical collecting ducts, facilitates potassium excretion. In principle, the lower urinary excretion of potassium and perhaps lower activity of the ENaC in blacks may arise from an augmented sodium reabsorption in tubular segments upstream to the location of ENaC. If so, reduced tubular flow and less sodium presentation to the ENaC would result in a lower activity of ENaC and less urinary potassium excretion in blacks. Two major sodium transport systems are located proximal to the main tubular site of the ENaC. These are the thiazide-sensitive Na-Cl cotransport and the furosemide sensitive Na-K-2Cl cotransport.

A primary increase in the activity of the Na-Cl cotransport system may result in: (1) low PRA caused by ECV expansion; (2) diminished potassium excretion because of reduced sodium delivery, and hence reduced tubular flow, to more distal tubular segments that are the main site of ENaC and potassium excretion; (3) diminished responses to amiloride; and (4) increased responses to thiazide diuretics. It seems that the clinical picture of sodium sensitivity in blacks fits these criteria, except that the heightened sensitivity of blacks to thiazide diuretics has been observed in terms of the blood pressure response, rather than in the urinary excretion of sodium and potassium.

Augmented Na-Cl cotransport activity should be marked by a greater natriuretic and kaliuretic responses to thiazide diuretics. In theory, during treatment with thiazide diuretics, ENaC activity may show a compensatory increase to reabsorb some of the sodium escaping reabsorption by the Na-Cl cotransport. In this way, small differences in Na-Cl cotransport activity between blacks and whites might escape detection if assessment of the cotransport activity is based only on the natriuretic response to thiazide diuretics. Chronic inhibition of Na-Cl cotransport by hydrochlorothiazide and Na-K-
2Cl cotransport by furosemide result in upregulation of ENaC expression in rats. This suggests that to decipher differences in activities of the Na-Cl cotransport and the Na-K-2Cl cotransport, one must focus on urinary potassium excretion in response to thiazide or loop diuretics. An increase in ENaC activity in response to these diuretics should increase the transepithelial electrical potential that drives potassium secretion into the tubular lumen. If Na-Cl cotransport activity were higher in blacks than in whites, then treatment with thiazide diuretics would induce a higher distal tubular flow and a greater increase in ENaC activity expressed as higher urinary potassium excretion in blacks than in whites. This was not found in a cohort of 9 blacks and 9 whites treated with hydrochlorothiazide. Treatment with the thiazide diuretic produced a comparable natriuretic response in both groups and actually increased the ethnic gap in urinary potassium excretion in relative and absolute terms. Before treatment, blacks excreted 11% (16.6 mmol/24 h) less potassium than did whites. However, during the 2 control days blacks excreted 31% (16.6 mmol/24 h) less potassium than did whites. Although the number of subjects was small, based on the available evidence, one cannot conclude at present that a primary increase in Na-Cl cotransport activity is a determinant of blacks’ sodium sensitivity. This tentative conclusion does not preclude a secondary involvement of the Na-Cl cotransport in this trait.

The Na-K-2Cl cotransport system functions primarily in the thick ascending limb of Henle’s loop, where it is central to the countercurrent mechanism, which is the process that establishes hypertonicity of the renal medulla and determines the ability to maximally concentrate urine. Can an increase in the activity of the Na-K-2Cl cotransport explain the lower PRA and urinary potassium excretion in blacks compared with whites? The answer to this question comes from observing the differences in urinary potassium excretion between blacks and whites in response to the inhibition of Na-K-2Cl cotransport by furosemide.

Luft et al examined the kaliuretic response of 347 normal subjects to furosemide. During 2 consecutive control days, 24-hour urinary potassium excretion was lower in blacks than in whites (day 1: blacks = 36.2 mmol, whites = 52.8 mmol; day 2: blacks = 42.1 mmol, whites = 62.8 mmol). After oral furosemide treatment, 24-hour urinary potassium excretion increased in both groups, but the potassium excretion remained lower in blacks than in whites (blacks = 68.7 mmol, whites = 82.9 mmol). Luft et al concluded that under control conditions and after furosemide treatment, blacks excreted less urinary potassium than did whites. However, during the 2 control days blacks excreted 31% (16.6 mmol/24 h) and 33% (20.7 mmol/24 h) less potassium than did whites. Whereas after furosemide, blacks excreted only 17% (14.2 mmol/24 h) less potassium. Indeed, furosemide caused a 74% increase in potassium excretion in blacks and only a 43% increase in potassium excretion in whites. Thus, in contrast to hydrochlorothiazide administration, which magnifies ethnic differences in the urinary potassium excretion, furosemide considerably narrows the racial gap. The conclusion we draw from Luft’s study is that the renal system of blacks is considerably more sensitive to furosemide than is that of whites. Thus, Na-K-2Cl cotransport in the thick ascending limb of Henle’s loop may be more active in blacks than in whites.

Models of increased Na-K-2Cl cotransport activity to explain sodium sensitivity in blacks. Left, Schematic presentation of approximate sites of the sodium transport mechanisms that are the focus of discussion in this article. Right, Two possible scenarios of increased Na-K-2Cl cotransport activity that may explain clinical and experimental observations of sodium sensitivity in blacks. Both scenarios represent a primary increase in the activity of the Na-K-2Cl cotransport without (scenario I) and with (scenario II) an expansion of the ECV. The ultimate effects of either scenario would be expressed by diminished urinary potassium excretion, increased sodium and water conservation capacity, and increased glomerular capillary hydraulic pressure leading to glomerular hyperfiltration (GFR that is inappropriately high for renal plasma flow). This would ultimately damage the glomeruli, a phenomenon that may contribute to hypertension. In addition, because of an increase in the filtration fraction, glomerular hyperfiltration would cause an increase in the colloid osmotic pressure in peritubular arterioles, promoting an increase in proximal tubular reabsorption.
Figure), or it may (scenario II in Figure). Because the ENaC is located distally to the main site of Na-K-2Cl cotransport, the ENaC may secondarily downregulate its activity when presented with less sodium caused by increased Na-K-2Cl cotransport activity. In this way, the final urinary excretion of sodium would match sodium intake despite increased Na-K-2Cl cotransport activity. Such secondary downregulation of the ENaC may result in a trade-off with respect to the renal excretion of potassium. A primary increase in the activity of the Na-K-2Cl cotransport would in itself diminish renal potassium excretion. However, a corresponding decline in ENaC activity, coupled with diminished tubular flow distally, would further decrease renal potassium excretion, explaining the lower urinary potassium excretion in blacks. Scenario I in the Figure is compatible with this physiological scheme. We suggest that the finding by Price et al25 that with low-sodium intake and a matched potassium intake, blacks excrete the same amount of urinary potassium as do whites support this concept. With high-sodium intake, the ENaC of blacks may be downregulated because of a high Na-K-2Cl cotransport activity. However, it is reasonable to expect that the activity of the ENaC would increase with low-sodium intake. This should promote an increase in urinary potassium excretion in blacks to match that in whites.

The observations that urinary potassium excretion is similar in blacks and whites when their diet is supplemented with potassium bicarbonate12,42 suggests that an increase in the distal delivery of bicarbonate would favor potassium excretion by raising the negative transepithelial electrical potential in the distal nephrons and cortical collecting ducts.50,51 In this regard, Morris et al44 proposed that potassium bicarbonate exerts antihypertensive effect by causing natriuresis. In addition, potassium bicarbonate supplementation may reduce availability of chloride to Na-K-2Cl in the thick ascending limb of Henle’s loop and thus enhances urinary potassium (and sodium) excretion in blacks.

How can a primary increase in the activity of Na-K-2Cl cotransport in the thick ascending limb of Henle’s loop without an expansion of the ECV account for low PRA in blacks? After all, the increased activity of this transport system would reduce the amount of sodium (chloride) presented to the macula densa, which by all accounts should result in an increase in the operating point on a high-sodium diet, resulting in an imbalance between the vascular tones of the afferent/efferent arterioles, leading to glomerular hyperfiltration; and an augmented proximal tubular reabsorption caused by glomerular hyperfiltration that would increase the colloid oncotic pressure in peritubular vessels. Because the model is based on indirect evidence, which is usually the case in clinical research, we are not definitive about it and do not pretend to be. Assuming that the model is correct, what do these features of sodium sensitivity in blacks mean? In addition, what are the broader ramifications of the model with regard to future clinical research?

Sodium sensitivity in blacks may turn out to be the outcome of race-related variation in not only sodium but also water metabolism. A primary increase in the activity of the Na-K-2Cl cotransporter would facilitate sodium conservation; however, by raising medullary hypertonicity it would also augment the capacity to better withstand water loss from extrarenal sources. Although a body of research exists regarding differences between blacks and whites with respect to sodium metabolism, little attention has been focused on racial differences in water metabolism. Recently, Bankir et al67 reported that young blacks have a greater ability to conserve water than do whites. They suggested that this racial difference may be attributed to vasopressin, because previous work had shown that older hypertensive blacks had higher vasopressin levels than did their white peers.68,69 However, Bankir’s subjects were 12 to 25 years old and presumably normotensive. We note, however, that vasopressin increases Na-K-2Cl cotransporter expression in the rodent thick ascending limb of Henle’s loop.70 Whether intrinsic renal mechanisms, hormones, or both account for differences between blacks and whites in the renal regulation of water, it is clear that the type of research conducted by Bankir et al67 is in order.

Attempts have been made to explain sodium sensitivity in general and in blacks in particular71,72 from the evolutionary...
perspective. An increase in the activity of the Na-K-2Cl cotransport in the thick ascending limb of Henle’s loop would render an optimal survival advantage because it facilitates not only sodium but also water conservation. Migrations out of Africa could have decreased selective pressure on such a system and could have led to the characteristics observed today in whites. Alternatively, genetic drift could have expunged genetic determinants of increased Na-K-2Cl cotransport in Europeans.

Natural selection operates principally during the reproductive years, whereas hypertension occurs primarily in older people. Hypertension, therefore, is unlikely to provide any selective advantage. However, the sodium sensitivity trait fits well with antagonistic pleiotropy, an evolutionary theory advancing the notion that some genes that render survival advantage during early years may ultimately become disadvantageous and cause disease in later years. In this sense, sodium-induced, progressive renal disease and hypertension in blacks are the lasting signature of an advantageous trait that has become disadvantageous in modern time.

Acknowledgments
The authors’ research on hypertension is supported by National Institutes of Health grants HL-47906, HL-63351 (AA), 5P50HL55000 (NKH), and HL-54512 (AW). We thank two anonymous reviewers whose suggestions considerably improved this paper.

References
Urinary Potassium Excretion and Sodium Sensitivity in Blacks
Abraham Aviv, Norman K. Hollenberg and Alan Weder

Hypertension. published online February 16, 2004;
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 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/early/2004/02/16/01.HYP.0000120155.48024.6f.citation

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

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

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