

Current Concepts in Hypertension

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Editor's Comments

As the largest professional society with an exclusive interest in the control of the world's most common disease, the American Society of Hypertension is pleased to provide this series of ASH Current Concepts in Hypertension. The latest in ASH's educational programs, each of these 6-page pamphlets will contain short reviews of 4 or 5 "hot" topics about the diagnosis and treatment of hypertension.

The involvement of the experts who are directly responsible for the new information and the rapid time from preparation to publication will ensure that these Updates will be of interest and value to every clinician who manages hypertensive patients.

Dr. William Frischman and I have been selected by the Society to edit these Updates. If the format is successful, more issues will surely follow.

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Upcoming Issues

Review of All Major Ongoing Antihypertensive Studies

Combination Therapies for Hypertension

Endothelial Function—Dyslipidemia

The Hottest Topic of the Moment

The August 23, 1995 issue of JAMA contained the data from the Puget Sound HMO's survey of drug use and myocardial infarction (Psaty et al. The risk of myocardial infarction associated with antihypertensive drug therapies. JAMA. 1995; 274:620-625). After the oral presentation of the data at the March 8 meeting of the Council for Cardiovascular Epidemiology, the media coverage was so one-sided and sensational, with headlines like Blood Pressure Drug Causes Heart Attack that even Dr. Psaty described the coverage as "a public health hazard."

This time the coverage was not as extensive and, instead of front-page scary headlines, the data were more reasonably presented along with the message from the accompanying JAMA editorial by Buring et al. Their message was clearly stated in the subtitle of their editorial: "A hypothesis formulated but not yet tested."

Buring pointed out the major limitation of this and all case-control studies. "The fact is that, in this design, primary healthcare providers selected particular patients for a given antihypertensive drug regimen. This self-selection is likely to have introduced at least modest biases into the results because of differences between those who were prescribed calcium channel blockers and those who were prescribed other antihypertensive medications."

Buring could have recalled the major scare of the 1970s over the claim that reserpine (then a very popular antihypertensive drug) caused breast cancer, based on case-control studies. This claim was subsequently shown to be absolutely wrong because—would you believe—it was based on "the biases of differences between those who were prescribed [reserpine] and those who were prescribed other antihypertensive medications."

So, let us remember the closing comments by Buring. "It would be particularly tragic if the large benefits of antihypertensive drug therapy are lost as a result of stopping medication because of an as yet unsubstantiated fear of an increased risk of myocardial infarction."

At the same time, Psaty's final comments seem sensible and worth repeating. "Ongoing large-scale clinical trials will assess the effect of various antihypertensive therapies, including calcium channel blockers, on several important cardiovascular outcomes. Until these results are available, the findings of this study support the current guidelines from the JNC, which recommend diuretics and β -blockers as first-line agents unless they are contraindicated, unacceptable, or not tolerated."

Sodium Intake and Myocardial Infarction in Hypertensive Patients

Patients treated for hypertension are frequently advised to curtail sodium intake. To determine the relationship between sodium intake and subsequent cardiovascular disease occurrence, the experience of 2937 mild or moderately hypertensive participants in a standardized work-site treatment program was examined. A 24-hour urine collection was obtained prior to initiation of therapy. Men differed significantly from women and were, therefore, analyzed separately after stratification into quartiles of urinary sodium excretion.

The distribution of race, smoking, personal or family history of cardiovascular disease (CVD), presence of left ventricular hypertrophy (LVH), and exposure to prior therapy was indistinguishable across quartiles. By contrast, the lowest sodium quartile included smaller persons with lower urine volume and potassium as well as sodium. Plasma renin activity varied inversely from sodium excretion while creatinine clearance varied directly. Mean systolic blood pressure did not vary but the highest sodium group had a higher diastolic blood pressure (1- to 2-mm Hg) than did the lowest. Standard laboratory values did not change over the study period. Blood pressure control was achieved equally by all groups in response to a modified stepped-care drug regimen, which was also similar in the subgroups.

urinary collection created a subgroup of 1298 men in whom these findings were replicated. Finally, in multivariate analysis, only age, cholesterol, plasma renin activity, LVH, current smoking (directly), and urinary sodium (inversely) were independently associated with MI and total CVD.

The principle finding in this prospective cohort study of successfully treated hypertensive subjects was a strong, step-wise, inverse association of sodium excretion with MI, primarily expressed in males. In any observational study—even a large, long-term, and carefully evaluated group—the possibility of confounding must be considered. Standard ascertainment of known cardiovascular risk factors and/or end-organ disease at entry revealed that relevant elements of history, laboratory, and physical examination did not cluster in the lowest sodium group. The single measure of 24-hour urine inevitably involves nondirectional misclassification of subjects which, in turn, leads to underestimation of the actual strength

These data should not be extrapolated to other populations

of the observed relationship. The hypothesis of this study was that, because a high plasma renin is associated with increased myocardial infarction and sodium intake is inversely related to plasma renin, a lower-sodium diet might increase CVD incidence. This hypothesis was sustained. In addition, however, sodium had a further independent association with MI.

Incidence of Myocardial Infarction According to Quartile of Urinary Sodium Excretion and Age in Men

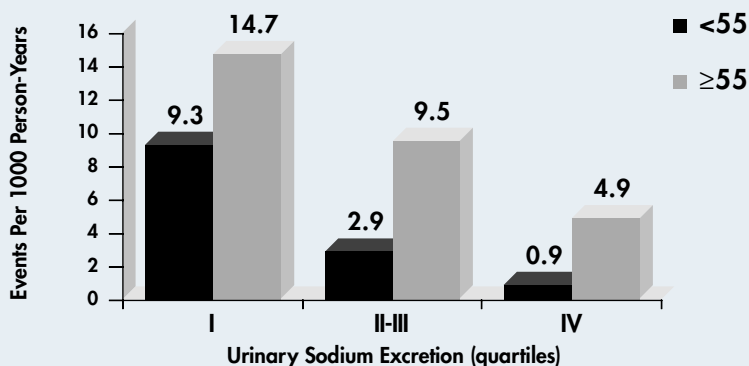


Figure 1

Relationship Between Sodium Excretion and Myocardial Infarction (MI)

During followup averaging 3.8 years, there were 96 cardiovascular events in men, and 21 in women. Of these, 46 and nine MIs, and 17 and six strokes, occurred in men and women, respectively. There was a step-wise and inverse relationship between sodium excretion and total cardiovascular disease as well as for MI (figure) in the group as a whole and in men, but not in women. By contrast, there was no association of sodium excretion to stroke or to noncardiovascular events. Application of a validated method to predict completeness of

In men, but not women, sodium excretion was inversely related to MI.

decisions. The need now is to confirm or refute the findings reported here.

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Hypertension. 1995; 25(6):1144-1152.

Implications

This is the first study linking sodium intake to subsequent cardiovascular health outcomes. Its results do not support current practice or public policy. These results, however, should not be taken out of context. First of all, participants were all successfully treated hypertensive subjects. Extrapolation to the normotensive or untreated hypertensive population is unjustified. Moreover, a single cohort study, regardless of the strength of its findings, can not establish causality or serve as the basis for clinical

Losartan

Because the renin-angiotensin system plays such a pivotal part in blood pressure regulation, there has been strong interest in treating hypertension with drugs that block critical actions of this system. Four sites for blockade are feasible (figure). Currently, the angiotensin converting enzyme (ACE) inhibitor, which prevents conversion of angiotensin I to the vasoconstrictor angiotensin II at site 3 is in wide clinical use.

Blocking receptors for angiotensin II (AT_2) at site 4 is another logical strategy. Losartan is the first orally administered drug to work at these receptors. Specifically, it blocks the AT_1 receptor which mediates the pressor actions of AT_2 on vascular tissue.

Clinical Characteristics of Losartan

Losartan provides effective 24-hour control of blood pressure when given in a once-daily dose. Although the parent compound has AT_1 -receptor blocking properties, an active metabolite of losartan produced in the liver is also a powerful receptor blocker and appears to be largely responsible for the prolonged duration of this agent's action.

Losartan has a narrow dosing range. For most patients a dose of 50 mg appears optimal. A lower dose is usually not clinically effective, whereas higher doses appear to add only minimal further efficacy. Studies with ambulatory blood pressure monitoring have confirmed the 50 mg dose of losartan can provide effective 24-hour blood pressure control.

In comparative studies losartan has had similar efficacy to ACE inhibitors or to β -blockers in patients with mild to moderate hypertension. The addition of a low dose of a diuretic to losartan provides clear additional efficacy, presumably because losartan can offset the unwanted stimulatory effects of diuretics on the renin-angiotensin system. For this reason, losartan is being made available not only as

monotherapy but also in combination with a low dose of hydrochlorothiazide.

Losartan is well tolerated and is free of the cough often seen with ACE inhibitors.

The renin-angiotensin system can be blocked at four sites.

One interesting feature of losartan is that it produces slight uricosuric effects.

Future Developments

It is appropriate to compare AT_1 blockers such as losartan with the well-established ACE inhibitors. One advantage of losartan is that it does not produce cough or angioedema. It has also been speculated that there are situations where ACE inhibitors cannot fully prevent AT_2 formation. For example, it is possible that the chymase system may provide an alternative pathway to ACE that cannot be effectively blocked by ACE inhibitors. The potential clinical importance of blocking AT_2 produced by non-ACE pathways—which presumably is accomplished by the new AT_1 receptor blockers—has yet to be evaluated.

Studies using losartan and other AT_1 receptor blockers have now been initiated in a variety of clinical situations. What are the effects of these agents on left ventricular structure and function in hypertensive patients? Will these effects be associated with improved outcomes? Similarly, will losartan and others in this new class have the renal protective effects that have been demonstrated with the ACE inhibitors? Research is now underway to examine these issues and to test the new agents for the treatment of congestive heart failure and other cardiovascular indications. There is growing interest in the ability of antihypertensive agents to influence long-term clinical events and survival, and the results of further research with losartan are keenly awaited.

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Renin-angiotensin System and Four Sites Where its Activity May be Inhibited

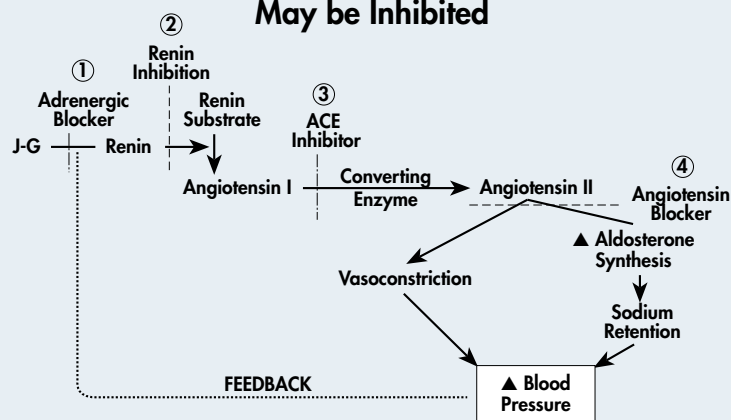


Figure 1

Renal Duplex Ultrasound for Diagnosis of Renal Artery Stenosis

Duplex ultrasound scanning of the renal arteries is a noninvasive screening test for the detection of renal artery stenosis. It combines direct visualization of the renal arteries (B-mode imaging) with measurement of various hemodynamic factors in the main renal arteries and within the kidney (Doppler), thus providing both an anatomic and functional assessment. Duplex scanning also allows the measurement of kidney size at the same time. Unlike other noninvasive tests, duplex scanning is not affected by medications that the patients may be taking, the level of renal function, or whether the disease is unilateral or bilateral or affects a solitary functioning kidney.

Comparison to Renal Arteriography

We prospectively studied 102 consecutive patients with both duplex ultrasound scanning of the renal arteries and renal arteriography. Patients were studied in the fasting state. All patients in the study had difficult-to-control hypertension, unexplained azotemia, or associated peripheral vascular disease giving them a high pretest likelihood of renovascular disease.

79% stenosis by arteriography ($P < 0.0001$). The resistive index (renal arterial impedance) within the kidney was elevated in 25 of 27 (93%) of arteries in patients with 80% to 99% stenosis of the renal artery and an end-diastolic velocity of < 150 cm/sec. We hypothesize that the end-diastolic velocity may not be increased in some patients with 80% to 99% stenosis because increased resistance (resistive index) within the renal circulation may have prevented an increase in end-diastolic velocity.

Advantages of Duplex Scanning

The advantages of duplex scanning of the renal arteries are that it is highly sensitive and specific for diagnosing significant renal artery stenosis. However, the technique is technically demanding and has a steep learning curve. Therefore, each vascular laboratory needs to correlate the results obtained from duplex ultrasound of the renal arteries with arteriography to ensure a reasonable degree of correlation. It is important to examine the renal artery from the anterior, lateral decubitus and, at times, posterior approaches so that all segments of the renal artery can be visualized and adequate Doppler samples obtained. Accessory renal arteries are difficult to identify and remain a limitation of the test.

The technique is technically demanding and has a steep learning curve.

Unlike captopril renography, duplex ultrasound is not dependent on whether the disease is unilateral, bilateral, or to a solitary functioning kidney, nor is it affected by the degree of azotemia present. Contrast media do not need to be administered so duplex scanning is a particularly useful test for screening azotemic patients in whom renal artery stenosis is suspected. It is also an

excellent test to follow patients serially who have undergone intervention (percutaneous transluminal angioplasty or stent) of the renal artery to identify restenosis or to follow the patient being treated medically for progression of disease.

The combination of direct visualization of the renal artery and Doppler assessment of blood flow velocity makes duplex scanning of the renal arteries an ideal screening test for the presence of renal artery stenosis in a population of patients with a high pre-test likelihood of renovascular disease.

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Ann Intern Med. 1995;122:833-838.

Comparison of Duplex Ultrasound with Arteriography

Ultrasound	% Stenosis by Arteriogram				Total
	0-59	60-79	80-99	100	
0-59	62	0	1	1	64
60-99	1	31	67	0	99
100	0	1	1	22	24
Total	63	32	69	23	187
Sensitivity	0.98		Positive Predictive Value	0.99	
Specificity	0.98		Negative Predictive Value	0.97	

Table 1

Sixty-two of 63 arteries that showed stenosis of $< 60\%$ using arteriography were correctly identified by duplex ultrasound scanning. Thirty-one of 32 arteries with 60% to 79% stenosis using arteriography were correctly identified as having 60% to 99% stenosis on duplex ultrasound and 67 of 69 arteries with 80% to 99% stenosis on arteriography were correctly identified as having 60% to 99% stenosis on ultrasound. Twenty-two of 23 arteries with occlusion on arteriography were correctly identified by duplex ultrasound.

Renal duplex sonography was 98% specific and sensitive.

The overall sensitivity of duplex ultrasound compared with arteriography was 0.98, the specificity was 0.98, the positive predictive value was 0.99, and the negative predictive value was 0.97 (table). When the end-diastolic velocity was 150 cm/sec or more, 81% of the arteries (38 of 47) had 80% to 99% stenosis while only 19% of the arteries (9 of 47) had 60% to

Alcohol and Blood Pressure

Excessive alcohol consumption has been held responsible for as much as 5% to 11% of all cases of hypertension seen in Western societies. The underlying mechanism relating heavy alcohol consumption to cardiovascular events is unclear. In animals, alcohol causes activation of the sympathetic nervous system and stimulates the release of corticotropin-releasing hormone (CRH), which has sympathoexcitatory effects when administered centrally.

Excessive alcohol causes 5% to 11% of hypertension.

Acute Effects on Sympathetic Activation

In a recent study of normal subjects we examined whether alcohol evokes sympathetic activation and whether such activation is attenuated by the inhibition of CRH release. We found that alcohol infusion (corresponding to two to three drinks) increased mean arterial pressure by roughly 10 mm Hg and markedly augmented the rate of discharge of sympathetic vasoconstrictor nerves targeted at the skeletal muscle vasculature, thereby indicating an important neural component of this alcohol-induced pressor effect (figure). After short-term dexamethasone administration the alcohol-induced sympathetic activation was no more detectable and alcohol infusion now

The acute pressor effects of alcohol involves sympathetic activation

caused vasodilation in the skeletal vasculature and a decrease in arterial pressure.

The importance of the alcohol-induced sympathetic activation in the mediation of the alcohol-induced pressor effect was further strengthened by studies using α -adrenergic blockade with phentolamine which had effects on blood pressure responses to alcohol infusion that were similar to those of dexamethasone.

Study Conclusion

This study provides several new conclusions. First of all, it demonstrates that in humans alcohol induces pressor effects by sympathetic activation that appears to be centrally mediated. Such sympathetically mediated pressor effects—possibly in conjunction with increased platelet aggregability could conceivably trigger acute alcohol-induced cardiovascular events. Second, the observation that dexamethasone suppresses the alcohol-induced increases in sympathetic activity (and blood pressure) suggests that an endogenous neuropeptide (CRH) modulates central sympathetic outflow and may play a role in the regulation of blood pressure.

Possible Long-term Effects

It is important to note that this study was designed to examine the neural and hemodynamic effects of acute alcohol administration in normal subjects and the results should not be extrapolated to reach conclusions regarding cardiovascular effects (and underlying mechanisms) of long-term regular alcohol consumption. It is likely that the long-term consequences of regular alcohol consumption reflect a balance between alcohol-induced cardioprotective effects (increase in high-density lipoprotein cholesterol, promotion of coronary vasodilation) and deleterious cardiovascular effects (stroke, hypertension). Since there is no evidence that drinking more than one to two drinks a day confers any cardiovascular benefits subjects who regularly consume alcohol beyond that level—independently whether or not they suffer from hypertension—should be advised to reduce their consumption. Whether sympathetic activation is one of the factors that also contributes to the long-term elevation of arterial pressure in subjects who drink alcohol every day needs further investigation but results from studies in rats suggest this could be the case.

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Effects of Alcohol Infusion in Normal Subjects (n=9)

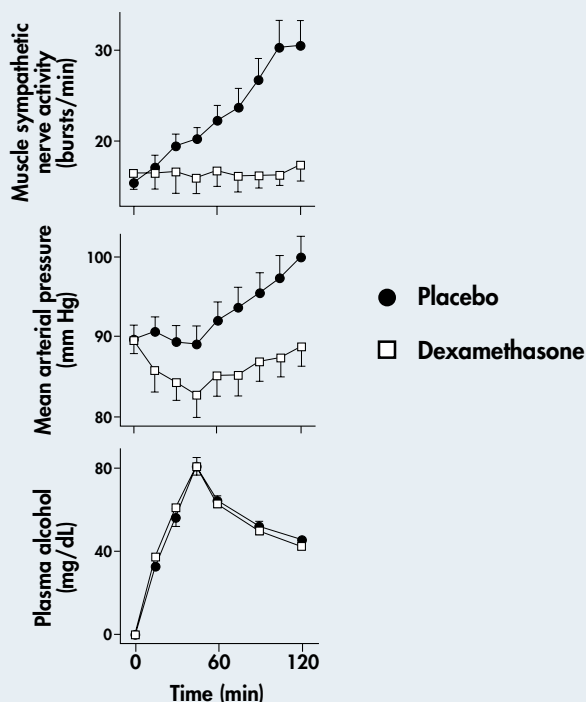


Figure 1

American Society of Hypertension

The American Society of Hypertension (ASH) is the largest US organization dedicated exclusively to hypertension and related cardiovascular disease. ASH was founded in 1985 by Dr. John Laragh and 16 other world-famous clinicians and scientists in an effort to evaluate the vast accumulation of data on hypertension and to provide a separate forum for those involved in the study or management of high blood pressure. The mission of the Society became “to organize and conduct educational activities designed to promote and encourage the development, advancement, and exchange of scientific information in all aspects of research, diagnosis, and treatment of hypertension, and related cardiovascular diseases.”

Today, the Society boasts a membership of over 3,000 strong with 95% of its members holding an MD, PhD, or other advanced degree. The Society continues to fulfill its mission by annual meetings that provide registrants with the rare opportunity to exchange information and ideas with more than 2,500 fellow scientists from around the world. Highlights of the meeting include state-of-the-art lectures by renowned faculty, plenary sessions, original communications, poster presentations, technical and scientific exhibits, and provocative special symposia.

In addition, the Society publishes the prestigious *American Journal of Hypertension*, a monthly publication containing the latest information in both basic science and clinical research.

Membership in ASH is open to all those who have undertaken and accomplished meritorious original scientific investigation in the field of hypertension and/or related cardiovascular disease, those involved in the diagnosis and treatment of hypertension and related cardiovascular disease, and those with a demonstrated serious interest in the field. Among the benefits of ASH membership are association and interaction with clinicians and scientists who are world leaders in the field, a subscription to the *American Journal of Hypertension* and all its supplements, a listing in the ASH Member Directory used for patient referral, and a savings of 50% or more on registration fees for the annual scientific meeting.

The American Society of Hypertension sponsors three award programs annually. The first award program focuses on the area of ongoing research training in the field of hypertension for young clinicians planning a career in academic medicine. Another recognizes and rewards three scientists who have carried out a significant body of work in the field of hypertension or related cardiovascular diseases. The last award program recognizes and rewards five young physicians, currently residents or fellows, who have a demonstrated interest in the study of hypertension or who plan a career change into the field.

The deadline for submitting applications for each of the above awards will be December 7, 1995.

For further information on ASH membership, awards programs, future meeting dates or to add your name to the ASH mailing list, contact:

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