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Canadian Cardiovascular Congress 2002

Usefulness of the Aldosterone-to-Renin Ratio for Screening Primary Aldosteronism

by Marcel Lebel. Presented at a Satellite Symposium of the Canadian Cardiovascular Congress, October 27, 2002 in Edmonton, Alberta.

Primary aldosteronism is characterized by hypertension, hypokalemia, high urinary potassium excretion, low renin levels, and elevated aldosterone production. In the past, the prevalence of primary aldosteronism among the hypertensive population was estimated to range from 0.5% to 2%. More recently, Gordon *et al* reported that 8.5% of the 199 normokalemic hypertensive patients in their study had primary aldosteronism. With improved screening

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Diastolic Dysfunction in Hypertensive Heart Disease

by Zion Sasson

Hypertensive heart disease is an end-organ consequence of systemic hypertension that manifests as myocardial stiffness and hypertrophy (also accelerating the development of atherosclerosis within the coronary vessels), generally presenting as left-ventricular hypertrophy (LVH) and LV diastolic and systolic dysfunction. The importance of diastolic function in hypertension and LVH is underscored in elderly individuals with congestive heart failure (CHF), when systolic function commonly is preserved and diastolic heart failure (HF) accounts for 50% to 60% of all cases. In fact, abnormalities of diastolic function may predict development of HF in the elderly.

Abnormalities of diastolic function can occur early in the course of hypertension and may precede detectable LVH. With time, interstitial mass and fibrosis increase in parallel with increasing LV mass and hypertrophy, influenced by blood pressure (BP) and other factors, such as age, obesity, diabetes, renin angiotensin and neuro-humoral stimulation, circulating insulin levels, dietary salt intake and renal sodium excretion. The 20% to 49% prevalence of LVH in hypertensive patients contrasts with the 80% prevalence of impaired diastolic function. The normal pattern of LV filling, quantified by measuring Doppler indices of transmitral flow, is characterized by rapid early filling in diastole termed E, with up to 20% additional filling during atrial contraction, termed A. Normal E/A ratio is > 1.0. Doppler interrogation of the pulmonary veins is used to quantify other variables of diastolic function, such

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Aldosteronism

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approaches—using the ratio of plasma aldosterone to renin levels—the average number of patients diagnosed with primary aldosteronism has increased considerably.

Screening Tests

For distinguishing patients with essential hypertension from those with primary aldosteronism, the 2001 Recommendations of the Canadian Hypertension Society advise to measure plasma aldosterone and plasma renin activity in order to estimate the ratio of plasma aldosterone to renin levels (aldosterone/renin ratio). Patients with an aldosterone/renin ratio greater than 550 pmol/L/ng/ml/h (S.I. units) or 20 ng/dl/ng/ml/h (conventional units) are suspected of having primary aldosteronism. Screening should be considered in clinical situations listed in Table 1.

Active Renin vs. Plasma Renin Activity

Until now, no reference values have been available for reporting the aldosterone/renin ratio using plasma aldosterone values expressed in international units (S.I. units, pmol/L) and the measurement of active renin (ng/L) by a mass assay immunometric method. Traditionally, plasma renin activity was measured indirectly by assessing the formation of angiotensin I *in vitro*, assuming that the angiotensinogen in the sample was normal. Direct immunometric assays of active renin were developed using specific monoclonal human renin antibodies. This method offers many advantages over the plasma renin activity procedure; these advantages include: 1) it is easier to standardize than the enzymatic assay, which can be altered by variations in the concentration of the endogenous angiotensinogen; 2) it has better inter- and intra-laboratory coefficients of variations and reproducibility that allows comparisons between different laboratories; and 3) angiotensin II more closely correlates with immunoreactive renin than renin activity.

Recent methods have improved sensitivity and can be used to assess suppressed renin levels. Because of these advantages, we consider that measurement of immuno-

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The True Relationship Between Sodium and Cardiovascular Disease

by Alain Vanasse and Geneviève Turgeon

Salt has long been a component of the human diet, yet questions about its role in the etiology of health problems are still under discussion. Salt has been used to preserve food for more than 6,000 years, and nearly 4,000 years ago the Chinese reported that "too much salt in food hardens the pulse." It was only in the early 20th century that reducing salt intake became a method for treating hypertension.[1]

In modern medicine today, studies are still being conducted—and articles published—on the relationship between high salt intake and cardiovascular (CV) risk. A study by Tuomilehto et al,[2] published in 2001, was conducted to show that high sodium intake increased the risk of acute CV events and mortality in the Finnish population. The results of this study are highly relevant since, in the West, 75% to 80% of the sodium consumed on a daily basis comes from prepared foods, and there is no Canadian legislation governing their labelling requirements or dietary composition. We also know that North Americans consume an excessive amount of salt. In Canada, the average daily intake is 5-7 grams, while Health Canada recommends between 2.5 and 4 grams.

Study Population and Design

The prospective study was conducted in Finland on two cohorts, one in 1982 and one in 1987. The initial randomized sample of 3,607 individuals aged 25-64 years was broken down into four age groups (25-34, 35-44, 45-54 and 55-64 years). After the exclusion of individuals for whom information was incomplete or non-existent, the analyses covered 1,173 men and 1,263 women.

Sodium intake was considered to be the independent variable, measured by 24-hour urinary sodium excretion. The other variables were age, blood pressure (BP), total and high-density lipoprotein (HDL) blood cholesterol, weight, height and smoking status. Data was collected using a standardized protocol similar to that of the World Health Organization's (WHO) MONICA project. The primary endpoints of the study were coronary events and non-fatal stroke, as well as death due to coronary disease, CV disease or any other cause. Data on these dependent variables were obtained from the hospitalization register for non-fatal events and from Statistics Finland for mortality data. International Classification of Diseases (ICD) codes were used: 410-414 for coronary deaths, 410-411 for non-fatal coronary events, 430-438 for stroke and 398-448 for CV death. Participants in the 1982 and 1987 cohorts were followed until the end of 1995.

Analyses and Results

Multivariate analyses were carried out using the Cox Proportional Hazards Model. Data on individuals who had reported a coronary event (28 men and six women) were excluded from the prospective analyses on coronary events; individuals reporting stroke (12 men and four women) were excluded from the prospective analyses on stroke. The relative risk associated with urinary sodium excretion was estimated for each 100 mmol increase in 24-hour urinary excretion. The analyses were adjusted for age and sex, as well as for the other cardiovascular risk factors (BP, total and HDL cholesterol, body mass index [BMI], smoking status).

The distribution of certain risk factors, such as age, total and HDL cholesterol and smoking, did not differ based on 24-hour sodium concentration quartiles, whereas systolic/ diastolic BP and BMI were higher in quartiles where urinary sodium excretion was higher. The average 24-hour sodium excretion was relatively high: 216 mmol (± 83) for males and 162 mmol (± 62) for females.

In males, the relative risk of death associated with an increase of 100 mmol in 24-hour urinary sodium excretion was 1.38 (95% CI, 1.04-1.82) for CV disease, 1.55 (95% CI, 1.12-2.13) for coronary disease and 1.30 (95% CI, 1.06-1.59) for other causes. These risks were significant. Similarly, the relative risk (RR) of coronary events was significant in males, in the order of 1.34 (95% CI, 1.06-1.70). This was not the case with stroke, for which the RR was 1.00 (95% CI, 0.68-1.47). Results for females showed a similar trend but were not significant due to the lack of power of the study invoked by the authors. However, the authors suggested that results obtained in the male population could be extrapolated to females. The authors also documented a significant increase in RR (1.44; 95% CI, 1.02-2.04) with respect to CV mortality in obese patients with higher urinary sodium excretion.

Conclusion

The study conducted by Tuomilehto et al showed that elevated 24-hour urinary sodium excretion is a predictor of coronary disease morbidity and mortality in males, independent of other CV risk factors (including BP). This relationship also is found in obese patients. However, the use of a 24-hour urinary sodium excretion measurement may not accurately reflect the average daily intake of sodium. If we add the results of this study to the sum of our present knowledge in this area, can it be said that these data on the nature of the relationship between sodium and CV disease are convincing? Previous publications on the results of the INTERSALT I and INTERSALT II studies, as well as on the DASH, NHANES and CARDIAC studies, reported certain findings that gained the general consensus of the scientific community and formed the basis for the position adopted by the AHA Nutrition Committee.[3] This acknowledges the harmful effect of excessive salt intake on BP, particularly in the obese. The Committee recommends that daily sodium intake should not exceed 6 grams for the general population and that it should be lower in the hypertensive population. The Committee considers these recommendations to be safe.

The principal topic of debate now concerns the risks associated with the restriction of dietary sodium in the general population. This situation persists because some publications suggest that there is a relationship between lower dietary sodium intake and a higher risk of CV events.[4] Although the methodology of such studies has been criticized, the fact

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Aldosteronism

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radiometric assays is the method of choice for measuring renin in humans.

Clinical Procedures

The following data is taken from an ongoing study in normotensive volunteers and hypertensive patients aimed at establishing reference values for the aldosterone (pmol/L) to active renin (ng/L) ratio. Blood samples for plasma aldosterone and renin measurements were drawn from ambulatory patients in the early morning (between 8:00 a.m. and 10:00 a.m.) at the outpatient clinic of the CHUQ, L'Hôtel-Dieu de Québec Hospital. The control group was recruited among normotensive subjects (blood pressure below 140/90 mmHg) coming for routine blood samples. Patients with a history of hypertension or diabetes, or with cardiac, hepatic or renal diseases, were excluded. Hypertensive patients had blood samples drawn for plasma aldosterone and active renin determinations while they were being investigated for hypertension.

Patients were diagnosed with essential hypertension when clinical and laboratory investigation excluded any secondary forms of hypertension. Most cases of primary aldosteronism were identified from those available in our Hypertension Clinic database. In patients with high aldosterone and low renin values, a definite diagnosis of primary aldosteronism was confirmed by demonstrating an inappropriate autonomous hypersecretion of aldosterone with captopril suppression and/or salt loading procedures followed by subtyping investigations. Spironolactone was discontinued at least six weeks prior to blood sampling. To avoid false positive results (Table 2), beta-bockers and clonidine were progressively withdrawn one week prior to the investigation, since an elevation of the aldosterone-renin ratio is predominantly an indicator of low renin. Post-synoptic angiotensin-I blockers, thiazide diuretics, calcium channel blockers and angiotensin II-converting enzyme (ACE) inhibitors were maintained when necessary to control hypertension. The morning dose was avoided prior to the renin-aldosterone measurements.

Table 1

Primary Aldosteronism: Who Should Be Screened

- Hypertensive patients with spontaneous hypokalemia
- Hypotensive patients with marked diuretic-induced hypokalemia
- Hypertension refractory to treatment with ≥ 3 drugs
- Patients found to have an incidentaloma
- All hypertensive patients?

Patients and Reference Values

A total of 206 subjects were included: 91 normotensive control subjects, 80 patients with essential hypertension and 35 patients with primary hypertension. Of those, 19 patients had surgically confirmed unique adenoma and 16 had presumed bilateral hyperplasia. All but one patient with essential hypertension had aldosterone/renin ratios below 100 (range 8 to 106); when measurement was repeated in this one exceptional patient, the ratio value of 106 decreased to 56. All primary aldosteronism patients had ratios above 140 (range 146 to 3,349). The mean aldosterone/renin ratio in normotensive controls was 41 ± 4 (range 2 to 118); four subjects had ratios above 100 (100.1, 103.5, 104.1 and 118). From these data, we extrapolated the preliminary reference values presented in Table 3. Essential hypertensive patients usually have aldosterone/renin ratios below 100, while ratios for patients with primary aldosteronism are above 140 combined with plasma aldosterone ≥ 400 pmol/L. Results that fall between 100 and 140 suggest a need for repeat testing.

It should be pointed out that a high aldosterone/renin ratio is not diagnostic by itself; primary aldosteronism must be confirmed by demonstrating an inappropriate autonomous hypersecretion of aldosterone. To this end, salt loading is widely used, but this approach may be contraindicated in patients with severe hypertension. The captopril-suppression test is safer, well-tolerated, and appears as effective as salt loading in confirming a diagnosis of primary aldosteronism.

Table 2

Aldosterone/renin Ratio

False (+)

- Beta-blockers
- Chronic renal failure
- Low renin hypertension
- Elderly patients

False (-)

- Spironolactone
- Severe hypokalemia

Table 3

Aldosterone/renin Ratio (pmol/L/ng/L)

• ≤ 100	Essential hypertension
• 100-140	Grey zone (repeat)
• ≥ 140	Primary aldosteronism (combined with plasma aldosterone > 400 pmol/L)

Conclusion

The random and ambulatory (morning) ratio of plasma aldosterone to renin values appears to be the preferred screening test for primary aldosteronism. This article presents reference values for reporting the aldosterone/renin ratio using plasma aldosterone concentrations expressed in SI units (pmol/L) and plasma active renin (ng/L) measured by radioimmunometric assay.

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Diastolic Dysfunction

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as the rate of deceleration of early diastolic flow (deceleration time) and different patterns of pulmonary venous flow.

Patterns of Abnormal Filling: A Continuum of Diastolic Dysfunction

Three abnormal patterns identify progressively greater impairment of diastolic function in hypertensive heart disease. The first pattern is termed "delayed relaxation," or mild diastolic dysfunction, when early LV filling is reduced, resulting in an E/A ratio of < 1.0. This pattern is seen in many patients with LVH and arterial hypertension who are generally asymptomatic since the left-atrial pressure is within normal limits. Vigorous atrial contraction—which may account for up to 70% of cardiac output—compensates for the reduced early filling.

The second pattern of abnormal filling is termed "pseudo-normal," or moderate diastolic dysfunction, when the E/A ratio is normal (> 1.0) but is distinguished from a true normal by a more rapid deceleration time and abnormal pulmonary venous flow. This pattern indicates increased LV diastolic chamber stiffness, and is associated with higher left-atrial pressure, commonly resulting in exertional dyspnea.

The third pattern of abnormal filling is termed "restrictive," and indicates severe diastolic dysfunction, when the E/A ratio is > 2.0, deceleration time is short with a markedly abnormal pulmonary venous flow pattern and little filling occurs during atrial contraction. Restrictive filling pattern is seen with marked elevation of left-atrial pressure and pulmonary congestion, and is associated with dyspnea at rest or with minimal exertion.

These three abnormal patterns of LV filling represent a continuum of increasing severity of diastolic performance, from asymptomatic patients (with delayed relaxation), to patients with exertional dyspnea (pseudo-normal pattern) and dyspnea on minimal exertion (restrictive pattern). Abnormalities of diastolic function have prognostic implications. In a population-based study of 2,042 randomly selected individuals in Minnesota, mild diastolic dysfunction was present in 21% of the overall population, and 6% had moderate or severe diastolic dysfunction with normal LV systolic function. These abnormalities were strongly predictive of overall mortality, with a eight-fold increased risk with mild diastolic dysfunction, and a 10-fold increased risk with moderate or severe diastolic dysfunction, compared to those with normal diastolic function.

Diastolic Dysfunction: Prevalence in Hypertension

Diastolic dysfunction is much more prevalent in the hypertensive population. In a recent study of 311 asymptomatic hypertensive patients, normal diastolic filling pattern was seen in only 13% of subjects, mild diastolic dysfunction was seen in 66% and moderate diastolic dysfunction in 21%. None had a restrictive pattern (not surprising, given their asymptomatic status). In a recent study of 1,839 hypertensive patients (53% men) with a mean age of 50.3 years, indices of diastolic function identified hypertensive patients at increased cardiovascular risk, independent of LV mass, level of BP, and ambulatory BP monitoring. The adjusted E/A ratio was the most powerful predictor of cardiovascular risk after age, diabetes and male gender. Thus, a low E/A ratio appears to be an independent marker of adverse prognosis in the general population, and this applies especially to patients with hypertension, presumably identifying those patients with increased interstitial fibrosis causing impairment of myocardial function.

Concentric LVH has been the most common type of hypertrophy documented in hypertenive subjects, with a relatively uniform increase in septal and free wall thickness and normal cavity size. There may be disproportionate septal thickening in 6% to 18% of hypertensive patients, with asymmetric septal hypertrophy, generally localized to the base to mid septum, at times overlapping with echocardiographic findings of hypertrophic cardiomyopathy. Commonly, this occurs in elderly hypertensive patients without severe diastolic abnormalities. In contrast, the term "hypertensive hypertrophic cardiomyopathy of the elderly" describes a substantial increase in LV thickness associated with small LV cavity, exaggerated systolic function and almost uniform impairment of diastolic function. This occurs more commonly in elderly women. Such patients often suffer from diastolic HF, presenting either in an acute decompensated state with CHF or in a more sub-acute or chronic stage with exertional dyspnea and fatigue relating to impaired diastolic function and reduced cardiac output.

CHF in the elderly is the leading cause of hospitalization in this age group, and a major cause of morbidity and mortality in Canada. Epidemiologic studies have shown that more than 50% of older patients presenting with CHF have diastolic HF with preserved LV systolic function. In a recent study of 129 consecutive patients older than 60 years with CHF, 59 had diastolic HF (with preserved LV systolic function, EF > 50%), and 60 had systolic HF (with EF < 35%). The clinical presentation and subsequent clinical course of each group was similar, with a severely reduced exercise capacity, neuro-endocrine activation and impaired quality of life.

The importance of diastolic function in hypertension and LVH is underscored in elderly individuals with CHF, when systolic function commonly is preserved and diastolic HF accounts for 50% to 60% of all cases. In fact, abnormalities of diastolic function may predict development of HF in the elderly.

Pharmacotherapy for Diastolic Dysfunction

For patients with moderate or severe LV diastolic dysfunction, the most effective means of reducing left-atrial pressure and improving symptoms over the short-term

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Ontario Chapter Annual Meeting Report

by Mansoor Husain

Drs. Duncan Stewart and Mansoor Husain, of the University of Toronto, co-chaired the 14th Annual Scientific Meeting of the Ontario Chapter of the Canadian Hypertension Society. The meeting was again held on the first weekend in May, and this year it returned to the beautiful Muskoka Sands Resort (now known as Taboo) in Gravenhurst, Ontario. The meeting was very well attended, with 147 registered attendees, of which 84 were delegates including family physicians, cardiologists, clinical pharmacologists, general internists, nephrologists, scientists and students from five Ontario Universities. The meeting would not have been possible without the financial support of the principal program sponsor (Pfizer Canada), major program sponsors (Aventis Pharma, Bristol Myers Squibb/Sanofi-Synthelabo, and Solvay), supporting sponsor (Boehringer Ingelheim) and the administrative excellence of Kathy Christmas (Queen's University).

In keeping with the tradition of this meeting, Drs. Stewart and Husain organized sessions that truly ranged from "bench to bedside." On Friday, Dr. Robert Ross (Queen's University) delivered a plenary session on "Influence of physical activity on obesity and related co-morbid conditions." Highlighted speakers for the Saturday sessions included Dr. Todd Anderson (University of Calgary) whose presentation was entitled "Antihypertensives and the potential vascular protective effects of anti-hypertensive agents," and Dr. Stephen Archer (University of Alberta), whose presentation was entitled "Experimental therapies for pulmonary hypertension 2003: recent and future additions to the vascular medicine tool kit—Viagra and Viruses."

This year's debate, "Be it resolved that hydrochlorothiazide should be the sole therapy approved for unrestricted use as first-line therapy for the treatment of hypertension," featured Dr. Ross Feldman vs. Dr. George Dresser (University of Western Ontario), and again proved lively. Finally, on Sunday morning, parallel workshops on topics of basic and clinical interest were led by Drs. Lowell Langille (University of Toronto) and Paula Harvey (University of Toronto), respectively.

The social agenda of this meeting also is worth mentioning. The faculty once again defeated the students in the annual basketball match.

During the Saturday-evening dinner, congratulations were extended to all of the trainees who presented their work at the meeting, and special poster and oral presentation prizes were awarded to the following trainees (by category and alphabetical order):

- Post-Doctoral Fellows: Robert Gros (Supervisor: Husain), and M. Golam Kabir (Supervisor: Husain);
- PhD Students: Taben Hale (Supervisor: Adams), Lynn Postovit (Supervisor: Graham), and Renee Suen (Supervisor: Stewart);
- MSc Students: Karolina Kolodziejska (Supervisor: Husain), Dorota Pszczolko (Supervisor: Langille), Steven Theriault (Supervisor: Van Huysse) and Eric van der Veer (Supervisor: Pickering); and
- B.Sc. Student: Johanna Hannan (Supervisor: Adams).

Dinner was followed by unrestrained dancing to the music of the Kingston-area band "Soul Survivor."

The next OHS Scientific meeting also is planned to be at Taboo, and will be held April 30-May 2, 2004.

Mansoor Husain, MD, FRCPC, Cardiology, Toronto General Hospital.

Diastolic Dysfunction

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is with diuretics, such as furosemide or hydrochlorothiazide. Long-term therapy should be aimed at lowering BP and regressing LV mass. With regression, LV diastolic function usually improves and cardiovascular morbidity decreases. Treatment with most classes of antihypertensive drugs has led to LVH regression, with the exception of agents that further stimulate sympathetic nervous system activity, such as direct vasodilators like hydralazine and minoxidil. Beta-blockers have less effective and less consistent results in LV mass regression. Diuretics, calcium entry blockers, angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have been reported to more consistently reverse LVH.

Despite the high prevalence of diastolic HF in the group of elderly patients with CHF, there are no randomized outcome studies of treatment. Retrospective analysis has suggested a potential benefit of ACE inhibitors or ARBs. Clinicians empirically use diuretics for symptomatic relief plus other anti-hypertensive therapy. The first of several large-scale clinical studies with primary endpoints of CHF recurrence and mortality, the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) study, has one arm of patients with diastolic HF and will be presented this fall.

Conclusion

In summary, diastolic dysfunction in patients with hypertension parallels increase in LV mass and LVH, and identifies a group at high cardiovascular risk. There is a continuum of severity of diastolic dysfunction that can be categorized into three patterns, identifying higher cardiovascular risk and symptomatic status. Patients with LVH and diastolic dysfunction are at the highest risk and require the most aggressive therapy.

Zion Sasson, MD, FRCPC, Cardiology, Mount Sinai Hospital and UHN, Toronto.

Blood Pressure Management in Acute Ischemic Stroke: The ACCESS Study

by R.I. Ogilvie

It has been recommended that treatment of acute hypertension in patients suffering an acute ischemic stroke be deferred, as acute hypotension may interfere with cerebral autoregulation, particularly surrounding the area of cerebral necrosis. Exceptions include patients requiring thrombolytic therapy, severe hypertension with systolic values > 220 mmHg or diastolic values > 120 mmHg, or concomitant conditions such as acute myocardial infarction (MI), left-ventricular failure, aortic dissection or malignant hypertension with recommendation of intravenous nitrates, nitroprusside or labetalol (depending on the clinical situation).

There have been few formal studies of patients without these concomitant conditions. The Intravenous Nimodipine West European Stroke Trial (INWEST) examined intravenous nimodipine, a calcium channel blocker, in acute ischemic stroke from 1994, and reported neurological deterioration as a consequence of acute hypotension. The Evaluation of Acute Candesartan Cilexetil Therapy in Stroke Survivors (ACCESS) recently was reported (*Stroke* 2003; 34:1699-1703) with some perhaps surprising results.

This was a multi-centre, randomized and placebo-controlled trial involving 342 acute stroke survivors. The trial was terminated prematurely because of positive results. Entry criteria included a motor deficit, a CT scan excluding cerebral hemorrhage, and systolic blood pressure (BP) > 180 mmHg and/or diastolic BP > 105 mmHg 24 to 36 hours after admission. Exclusion criteria included age > 85 years, disordered consciousness, internal carotid artery stenosis > 70%, malignant hypertension, heart failure, unstable angina or high-grade aortic or mitral stenosis. The target reduction in BP was 10% to 15% within 24 hours.

The study onset averaged 29.8 hours after the onset of symptoms. The BP in the candesartan-treated group was not different from the placebo-treated group at the onset (188/99 vs. 190/99 mmHg) or at the end of the first week. No significant event occurred as a result of hypotension. At the end of the first week, a 24-hour ambulatory BP record was obtained. Patients assigned to candesartan were continued on this drug and followed for 12 months. Patients assigned to receive placebo for the first week were started on candesartan therapy if their mean daytime BP was > 135/85 mmHg (166/168 patients). Both groups had their candesartan dose adjusted and other drugs added (thiazide, felodipine or metoprolol) to maintain office BP < 140/90 mmHg or ambulatory daytime averages < 135/85 mmHg. BPs of the two groups did not differ at the end of the 12-month follow-up.

Thus, the only difference between the two groups was that one received placebo for seven days after the acute stroke event, as both received candesartan after the first week and achieved similar BP reduction. Yet, at the end of 12 months, 18.7% of the seven-day placebo group had experienced a vascular event in contrast to 9.8% of the first-seven-day candesartin group. These included 10 fatal and non-fatal CV events in the placebo group versus two in the candesartan group, and 19 fatal and non-fatal cerebrovascular events in the placebo group versus 13 in the candesartan group.

The number of events in the two groups significantly diverged after 100 days in the study, mainly due to a lower number of myocardial ischemic events. The reason for this surprising result in unclear, but some early effect on vascular remodeling may be involved. It is clear that cerebral autoregulation was not impaired by administration of candesartan within a few days of an acute ischemic stroke with severe hypertension and that long-term benefit ensued. Hopefully, additional studies of BP management in the acute phase of ischemic stroke will be undertaken.

R.I. Ogilvie, MD, FRCPC, FACP, Hypertension Unit, The Toronto Western Hospital.

Sodium and CV Disease

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remains that the results presented need to be confirmed or refuted before appropriate measures can be put forward for the population at large. Unfortunately, the results presented in the article by Tuomilehto et al do not allow us to do this. On the other hand, experience in Finland over the past 20 years or more, which has led to a national public health policy on the reduction of dietary sodium intake, gives us a perspective of the population that goes beyond clinical experimentation. The Finns have periodically evaluated the measures they have taken and have published the results, which suggest that a reduction in dietary sodium for the population as a whole would be safe and may even have a positive impact. However, the debate surrounding the effects of sodium on health goes beyond scientific boundaries and is subject to non-scientific imperatives that are difficult to delineate. Thus, the influence of the Salt Institute[5] and its lobbyists cannot be ignored, as shown by the recent events and demonstrations that have taken place in France with respect to a government proposal regarding the regulation of salt.

Should we plan to promote measures comparable to those adopted in Finland? Would such action be possible in the context of Canadian legislation? Such questions deserve the particular attention of Canadian scientists and lawmakers.

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Microalbuminuria in Hypertensives Without Diabetes: A Prognostic Marker for Vascular Events

by R.I. Ogilvie

In diabetes, the presence of proteinuria > 300 mg/day is associated with increased mortality and morbidity from cardiac, cerebrovascular and renal events. Microalbuminuria (MAU) with protein loss between 30 and 300 mg/day also is a marker for these events in both type 1 and type 2 diabetics. Although 24-hour urine collections should be used to confirm the amount of proteinuria or MAU and creatinine content a first-morning-void urine sample is more practical as a screening test examining the ratio of microalbumin/creatinine. In diabetes, the diagnosis for MAU is an albumin/creatinine (mg/mmol) ratio of 2.0 in men or 2.8 in women. However, these cut-off threshold ratios may be too high and there are many who argue that MAU is a continuous risk indicator. The same argument has been made for both blood pressure (BP) and low-density lipoprotein (LDL) cholesterol, especially in diabetic patients.

For at least six decades, it has been reported that MAU in the absence of diabetes also is associated with premature vascular events. Depending on the definition used, the prevalence of MAU is approximately 5% in subjects without diabetes or hypertension and approximately 5% to 20% in hypertensives without diabetes. There have been several reasonably large populations studied showing association between MAU with increased office and ambulatory BP, non-dipping reduction in overnight BP, pulse pressure, increased body weight, salt sensitivity, high sodium diets, dyslipidemia, insulin resistance, smoking, post-menopausal state, and electrocardiogram (ECG) or echocardiographic evidence for left-ventricular hypertension (LVH). All of these are known risk factors for premature vascular events. The pathophysiological mechanism underlying MAU is not established, but likely reflects generalized endothelial dysfunction interplaying with intra-glomerular pressure. Insulin resistance can augment MAU but is not necessary for its occurrence.

MAU in the first three days after acute myocardial infarction (MI) has been used to predict in-hospital mortality. There are several prospective studies of non-diabetic individuals with or without hypertension, demonstrating a relationship between MAU and premature vascular events and mortality. What may be surprising is that the threshold microalbumin/creatinine ratio in these studies has been lower than the 2.0 mg/mmol ratio used to define renal disease in diabetics. Three recent publications have reported ratios of > 0.67, 1.01 and 1.07 as predictive of ischemic cardiac disease. The Heart Outcomes Prevention Evaluation (HOPE) study results suggest the absence of a threshold effect. For every 0.4 mg/mmol increase in the ratio above 0.22, the adjusted hazard of major CV events increased by 5.9% in both diabetic and non-diabetic participants followed for a median of 4.5 years regardless of BP, cholesterol or treatment. This places MAU along with BP and LDL-cholesterol values as independent and continuous risk factors (rather than having threshold values).

Thus, measurement of the microalbumin/creatinine ratio in hypertensive subjects without diabetes likely would aid in identifying individuals at higher risk for premature vascular events. Studies that assess the effect of antihypertensive treatment on MAU and endpoints of vascular morbidity and mortality are required. We also need studies to determine if different drug classes have a differential effect on MAU and vascular endpoints. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) appear to be effective in reducing albuminuria but it is not clear that they are more effective in preventing vascular endpoints in non-diabetic patients. For example, the Losartan Intervention for Endpoint Reduction (LIFE) trial of older hypertensive patients with ECG-LVH assigned to either atenolol or losartan demonstrated a better outcome with the ARB. It would be of interest to learn if the subjects with MAU in this trial had different outcomes according to assigned therapy. Perhaps reduction in MAU will become a surrogate endpoint for adequacy of antihypertensive drug treatment. In the absence of definitive studies, I have begun to use the presence of MAU (arbitrarily defined as > 1.0 mg/mmol) as an aid to persuading my patients to adhere to both drug and non-drug measures for BP control. It helps me to target individuals at higher risk for whom I believe intervention would bring the biggest benefit.

Additional Reading:

1. Borch-Johnson K, et al. Urinary albumin excretion: an independent predictor of ischemic heart disease. Arterioscler Thromb Vasc Biol 1999; 9:1992-7.
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4. Gerstein H, et al. Albuminuria and the risk of cardiovascular events, death, and the risk of heart failure in diabetic and non-diabetic individuals. JAMA 2001; 286:421-6.
5. Wachtell K, et al. Urine albumin/creatinine ratio and echocardiographic left ventricular structure and function in hypertensive patients with electrocardiographic left ventricular hypertrophy: The LIFE study. Am Heart J 2002; 143:319-26.

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