Types of Headache in Hypertensive Individuals

More than 90% of people experience headache of some kind at least once in their lifetime. Many patients and physicians still believe headache to be a common symptom of hypertension. Pathophysiologically, a headache arises when the primary afferent fibers that innervate the meningeal or cerebral blood vessels are activated; most of these nociceptive fibers are located within the first division of the trigeminal ganglia or upper cervical ganglia. Although patients with secondary headache disorders have, by definition, an identifiable structural or inflammatory source, most chronic headaches are primary headache disorders such as migraine or tension headache. The prevalence of migraine and tension headaches, the most common cause of chronic headache, in the hypertensive population at large is not known. Migraine, a disorder of neurovascular regulation with a central nervous system generator, is broadly categorized as migraine without an aura (85%) and migraine with an aura (i.e., classic migraine, affecting 15% of patients).

Differentiation between a primary and secondary headache disorder often necessitates a detailed history, particularly since an individual patient can suffer from different types of headaches. To determine whether headache in a hypertensive patient is due to elevated blood pressure (BP) and not to other causes of headache can be a time-consuming and challenging task. Migraine is more prevalent in younger adults, whereas hypertension increases with age. Since hypertension and migraine headaches are both common disorders affecting 10% to 22% of the adult population, one can expect up to 3% of the population to have both conditions.

Hypertension and Headache: Effect or Coincidence?

In 1913, Janeway drew attention to the association between headache and severe hypertension. Subsequently, larger epidemiological studies showed no difference in the prevalence of headache between hypertensive and non-hypertensive populations. Nevertheless, some clinical studies have reported that headache was more common in hypertensive patients, particularly in severe or untreated hypertension. In 1988, the International Headache Society reached agreement that chronic arterial hypertension of mild-to-moderate degree does not cause headache.

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According to the International Classification of Headache disorders (2004), headache can be caused by severe hypertension associated with pheochromocytoma, hypertensive crisis with or without hypertensive encephalopathy, preeclampsia and eclampsia, and acute pressor response to exogenous agents. These headaches are usually pulsatile and located over the occipital area, but may be frontal (especially in children) or generalized. The headache is often present upon awakening in the morning. More than 50 years ago, Stewart observed that patients complained of headaches more often after they had been made aware of the diagnosis of hypertension.

The physiologic mechanisms involved in the causation of headaches in acute and chronic hypertension remain unclear and controversial. It has also been reported that uncontrolled hypertension can increase the frequency and severity of migraine attacks, or even transform an episodic form of migraine into a chronic daily headache.

In a survey of 22,685 Norwegian adults whose BP had been measured 11-years earlier, Hagen et al found that individuals with a systolic BP greater than 150 mmHg had a 30% lower risk of non-migrainous headache compared to those with a systolic BP less than 140 mmHg. Moreover, the risk of non-migrainous headache decreased with increasing diastolic levels. Those findings were applicable to both sexes, regardless of whether they were receiving antihypertensive medication. Legal delivery second quarter 2006. Articles may be submitted, in either English or French, to the Editorial Office, Hypertension Canada, The Toronto Western Hospital, University Health Network, 399 Bathurst St, Toronto, Ontario, M5T 2S6. FAX: (416) 603-7919. Deadline for submissions for the next issue is September 2006. Canadian Publications Mail Sales Product Agreement #40063348.

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have lower BP than those without migraine. This inverse relationship between BP levels and headache has been attributed to the phenomenon of “hypertension-induced hypalgesia,” whereby sensitivity to painful stimuli has been shown experimentally to correlate inversely with BP levels. Ghione had proposed that this could be due to a resetting of the baroreflex activity in nociceptive modulation.

Drug-induced Headache
Headache is a commonly listed adverse effect of most antihypertensive drugs, especially the calcium channel blockers (CCBs) and direct vasodilators such as hydralazine. If a patient receiving antihypertensive therapy develops or complains of worsening headache, the temporal association between the start of a particular drug and the headache can help decide on a trial withdrawal of the drug with close observation of BP. However, many hypertensive patients are frequently taking other drugs that also can cause headaches, some (e.g., nitrates) more frequently than others (e.g., statins).

Headache in Antihypertensive Drug Trials
In an analysis of data from seven clinical trials comprising 2,673 patients with mild-to-moderate hypertension treated with irbesartan, Hansen et al reported that patients treated with the angiotensin-receptor blocker (ARB) had significantly lower incidence of headache compared to those taking placebo (17% vs. 22%).

Law et al performed a meta-analysis of 94 randomized, placebo-controlled trials including a total of 24,000 participants in whom thiazides, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors and ARBs were used at fixed doses. Across all of the trials, about one third of the participants were allocated to placebo groups. Antihypertensive drug therapy lowered systolic and diastolic BP by 9.5 and 5.5 mmHg, respectively. About one third fewer individuals in the antihypertensive-treated groups reported having headaches compared to placebo. The authors estimated that one in 30 treated patients benefited by having headache prevented. Headache reduction occurred with each of the four classes of drugs. BP-lowering reduced headaches by a constant proportion, irrespective of initial prevalence. Since headache reduction occurred with pharmacologically diverse classes of drugs, BP reduction itself was considered the likely cause for the benefit.

These investigators implied that elevated BP caused headache in some patients with mild-to-moderate hypertension. However, since both studies did not specify which type of headache was being recorded, it is possible that antihypertensive drug therapy was providing relief for more specific types of headache, such as migraine. The effect of antihypertensive drugs on tension headaches is unknown.

ACE inhibitors, ARBs and Migraine
Certain beta-adrenergic blockers (e.g., propanolol, metoprolol, atenolol, timolol and nadolol) and calcium blockers, such as verapamil, have an established role in migraine prophylaxis. Migraineurs with the ACE DD genotype have been shown to have elevated plasma concentration of ACE compared to those with the II and ID genotypes. The frequency of migraine attacks was found to be higher in those with DD as compared to ID and II phenotypes. More recent studies of ARBs provide plausibility to the notion that increased availability of angiotensin II could play a pathogenetic role in migraine headaches. In a meta-analysis of 27 studies (N = 12,110) including seven different ARBs, treatment of patients whose diastolic BP ranged from 95 to 115 mmHg with ARBs resulted in a 31% reduction in the frequency of reported headache (NNT = 21). This

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Retinal Vessels as a Target Organ in Hypertension

By Carl Abbott

There is more to hypertension than elevated blood pressure (BP). That is why all hypertension guidelines recommend target-organ (brain, eyes, heart, kidneys and peripheral vessels) assessment in the initial overall evaluation of patients with suspected hypertension and as part of the management strategy.

Some target-organ damage (TOD) or reversible dysfunction can be ascertained by history alone (previous stroke, transient ischemic attack [TIA], angina or myocardial infarction [MI], intermittent claudication, etc.) but physical examination is needed to identify retinal-vessel abnormalities and to confirm brain or cardiac dysfunction, weak pulses and differences between brachial and ankle BPs.

Laboratory function tests and imaging are used to reveal abnormalities of kidney function. The 12-lead ECG (and sometimes the echocardiogram) completes the picture. Visual complaints cannot be relied upon to predict funduscopic changes in hypertension.

As medical students, we are taught (with varying exposure and intensity) how to examine the optic fundus because it is an essential part of the examination for some patients depending on their problem. Unfortunately, facility in the art of funduscopy varies. For ongoing evaluation of patients with diabetes mellitus, funduscopy is an essential regular examination to monitor for diabetic and hypertensive changes. The year of graduation often determines which classification of hypertensive changes we use. In 1939, Keith, Wagener and Barker suggested a classification system that endured for many years. Their four “grades” were used for predicting patient prognosis at a time antihypertensive treatment was virtually non-existent. Some physicians simply described the changes for the medical record. Retinal exudates and hemorrhages were rarely missed even through undilated pupils, but the presence or absence of papilledema in a given patient was often cause for uncertainty and discussion on ward rounds. The hospital ophthalmologist was called, dilated the pupils and gave the last word. The retina is the sole area where arterioles and veins can be seen, so we were taught—and always assumed—that examination of these retinal vessels was useful, perhaps predictive of duration and severity of hypertension, even reflecting the state of the vasculature elsewhere (in contrast to diabetes mellitus, a poor association seems to exist with renal pathology). Finding no retinal abnormalities was considered a good sign in hypertension, and in recent times has been used to support a diagnosis of office-induced (or white-coat) hypertension. Finding only “early vessel changes” could be comforting to the doctor and patient. But was funduscopic examination really useful? Retinal photography with a fundal camera soon allowed ophthalmologists to see earlier hypertensive changes than had been possible with the ophthalmoscope.

In 1995, Fuchs et al questioned the usefulness of optic fundus examination when used by internists and cardiologists working in a hypertension clinic in Brazil. Pupils were dilated and a simplified Keith-Wagener (KW) classification was used in 400 patients, most of whom were receiving antihypertensive therapy. None had diabetes mellitus. Fundus abnormalities (of any kind) were infrequently seen, being observed in only 12% of patients with “less severe hypertension” (some of whom may have had white-coat hypertension). Even in those with “severe hypertension” (defined as DBP > 105 mmHg, SBP > 180 mmHg, for a duration > 3 years), the frequency of abnormality was only 41%. Grades I and II KW changes were poor predictors of severity of hypertension in this study. The authors considered arteriolar narrowing to be a manifestation of atherosclerosis, increasing with age. AV crossing changes were more suggestive of high systolic pressure.

Not everyone would agree with these conclusions. Dodson et al offers a simpler grading system which appeals to me and includes only strictly hypertensive changes:

- **Grade A (“non-malignant” hypertension):** generalized narrowing or focal vasoconstriction; AV nicking not included. These changes may be determined by the level of BP but age and other factors (e.g., lipid profile) are important.
- **Grade B (“malignant” or accelerated hypertension):** Hemorrhages, hard exudates and cotton wool spots with/without optic disc swelling.

Recently, Ikram et al measured retinal vessel diameters using digitized retinal photography in 6,436 people in Rotterdam, aged 55 years or older, followed for a mean of 6.6 years. Subjects were classified as: a) having normal BP...
Hypertension (< 130/80 mmHg); b) having pre-hypertension (120-139/80-89 mmHg); or c) otherwise having hypertension. Some (4%) reported diabetes mellitus. The measurements yielded an arteriolar:venular ratio (AVR). Reductions in AVR during follow-up were predictive of the development of hypertension but arteriolar narrowing alone was a more sensitive measure, as narrowing of venules also occurred with hypertension. The investigators concluded that generalized retinal arteriolar narrowing may precede the development of hypertension, and that isolated generalized narrowing was more strongly predictive of risk of hypertension than reduction in AVR.

What do current textbooks on hypertension advise? The *Manual of Hypertension*, edited by Mancia et al, states "the description of hypertensive retinopathy in the evaluation of the hypertensive is hallowed by time but notoriously inaccurate." Kaplan, in his *Hypertension* textbook, advocates use of the ophthalmoscope but concludes, "in non-ophthalmologic clinical practice, however, funduscopic findings are of limited value, having only about a 60% +/- predictive value for the severity of the HT."

Is advanced retinopathy currently less prevalent? While many with hypertension still remain untreated or under-treated, the MONICA study notes a reduction in frequency of hypertension worldwide in the past 25 years, unrelated to pharmacologic intervention. Some populations dif-

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Announcement

Two New Patient Guides Available

*My Nutrition Guide for the Prevention and Treatment of High Blood Pressure* is a 60-page outline in seven chapters including information in point-form about the DASH diet, reducing sodium intake, alcohol, healthy food choices, dietary fibre, weight-control, natural products and drugs, with advice on reading food labels, restaurant meals and some eye- and taste-appealing recipes for home cooking. It was prepared by dieticians specialized in cardiovascular care.

*Questions and Answers. A Patient’s Guide to Controlling Hypertension* is a 70-page booklet with 18 chapters answering patients’ common questions about how blood pressure is measured, self-measurements, target values, tests involved in diagnosis, hypertension and insurance, lifestyle changes for prevention and control, exercise recommendations, types of drugs used and their side effects, natural products and blood pressure, aging and blood pressure, and much more. It was prepared by a group of health professionals, doctors, pharmacists and nurses specialized in cardiovascular care.

These guides are an initiative of the Quebec Hypertension Society in collaboration with the Canadian Hypertension Society, with Drs. Denis Drouin and Alain Milot as Chief Editors. Versions in French or English are available for $19.95 each by contacting:

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Cerebrovascular disease (CBVD) is among the most significant causes of mortality. In addition, current demographic changes tend to show that the prevalence of CBVD will rise in the coming years. It has now been clearly shown that arterial hypertension is the prime risk factor for the occurrence of stroke. Numerous studies have proven that a reduction in blood pressure (BP) reduces the risk of a CBVD event by about 40%. In particular, studies involving elderly patients with predominantly systolic hypertension have demonstrated the benefits of reducing the incidence of CBVD events using various classes of antihypertensive agents.

**Background**

Although the benefits of employing antihypertensive agents as primary prevention in reducing the incidence of CBVD events appear clear, few studies have documented the advantages of this approach as a secondary-prevention tool in hypertensive patients. The Perindopril Protection Against Recurrent Stroke Study (PROGRESS), published a few years ago, demonstrated an impact on this type of patient. It was conducted among a population of hypertensive and normotensive patients with a history of stroke or transient ischemic attack (TIA). The study compared an ACE inhibitor (perindopril), administered alone or with a thiazide diuretic (indapamide), versus a placebo. At the end of the follow-up period, the active treatment resulted in a significant reduction in the recurrence of new events (of approximately 28%). It was, however, concluded that the benefits were significantly related to the ACE inhibitor/diuretic combination, rather than to either individual component. The patient subgroup randomized to this combination therapy experienced a 43% reduction in the risk of new events, together with a reduction in systolic/diastolic BP of 12/5 mmHg. The results of this study had such an impact that they were incorporated into the Canadian hypertension guidelines, which thereafter recommended the use of an ACE inhibitor/diuretic combination for secondary prevention in patients who had already presented with a TIA or stroke.

**MOSES Study: Methodology**

No other large-scale study examined this issue further from that point on, particularly in a hypertensive patient population. The Morbidity and Mortality After Stroke, Eprosartan Compared With Nitrendipine for Secondary Prevention (MOSES) study, published last year, represented the first study in which morbidity and mortality outcomes were considered in patients with high BP and a history of stroke or TIA. The principal objective of this study was to assess the efficacy of treatment based on eprosartan, an angiotensin II receptor blocker (ARB), versus nitrendipine, a dihydropyridine calcium channel blocker (DHP-CCB) not marketed in Canada (which had demonstrated its efficacy with regard to primary prevention in the SYST-EUR study involving patients older than 60 years of age presenting with isolated systolic hypertension). The two treatments were compared with respect to their ability to prevent recurrent cerebrovascular events. A total of 1,405 hypertensive patients who had had a stroke or TIA within the past 24 months were included in the study. The events were objectively confirmed by magnetic resonance imaging (MRI) or computed tomography (CT) scan. At the end of a mean follow-up period of 2.5 years, both treatment groups were compared with respect to the primary outcome, defined as a combination of total mortality and all cerebral or cardiac events.

**MOSES Study: Results**

The BP of more than 75% of patients in each treatment group returned to normal (< 140/90 mmHg) after three months, and was maintained until the end of the study. The decrease in BP obtained in the two groups was approximately 16/8 mmHg. Despite a similar decrease in BP, the eprosartan group experienced fewer events compared to the nitrendipine group (206 vs. 255; relative risk 0.79; 95% CI 0.66-0.96; p = 0.014). There was a non-significant 25% decrease in cardiac events with eprosartan (77 vs. 101; p = 0.061) and a 25% decrease in cerebrovascular events (102 vs. 134; p = 0.026). However, if TIs (66 vs. 92 for eprosartan vs. nitrendipine, respective-
ly) were excluded from such events, the difference between the two treatment groups was no longer significant as far as ischemic/hemorrhagic stroke was concerned (36 vs. 42). In addition, if only the first events in all patients were considered, there was a total of 169 events, with a non-significant difference between the groups (80 vs. 89; \( p = 0.42 \)). Finally, no difference in mortality was observed between the two study groups.

**Discussion of MOSES Results**

Upon analysis, there are many positive aspects to the results of the MOSES study. One of the principal qualities of this study is that a similar reduction in BP was obtained in both treatment groups. This methodological factor is crucial when assessing an outcome that is chiefly influenced by the extent of the decrease in BP. In addition, target BP was achieved in a large proportion of patients. More than 75% of patients in both treatment groups became normotensive (< 145/90 mmHg). Based on the equivalence of the reductions in BP and the significantly different results with regard to the primary outcome, should it be concluded that ARB-based treatment is superior in this type of patient?

During the study, the vast majority of patients required treatment with combination therapy. In the eprosartan group, the use of ACE inhibitors was two times less frequent than in the nitrendipine group (11.3% vs. 21%), whereas calcium blockers were used two times more frequently (14.4% vs. 7.5%). Some studies, like the Blood Pressure Lowering Treatment Trialists’ Collaboration meta-analysis, have concluded that CCBs may have a protective effect with respect to cerebrovascular events, and this might partially explain the benefits seen in the eprosartan group. Likewise, the more frequent use of ACE inhibitors in the nitrendipine group may explain the lack of any significant difference with regard to cardiovascular events.

However, despite the differences attributable to one pharmacologic agent compared to another, the MOSES study was criticized for methodological flaws, particularly with regard to TIA diagnosis. As mentioned previously, TIAs were the most prevalent events (67%) and thus had an important influence on the study’s results. Two particular criticisms were made concerning the inclusion of TIAs in the principal assessment parameter. First, such a diagnosis is often subject to interpretation and, second, recurrent events (the possibility of more than one event per patient) were included in the primary outcome analysis.

It now appears that the MOSES study’s conclusions that eprosartan is superior to nitrendipine are not adequately supported by the study data. After examining convincing data drawn from the study, the Canadian Hypertension Education Program (CHEP) revised its guidelines in 2006: it no longer recommends the use of ARBs as secondary prevention for stroke/TIA, and continues to support an ACE inhibitor/diuretic combination.

**Summary**

Despite certain methodological flaws, the results of the MOSES study tend to show that ARBs may confer a certain degree of stroke prevention over and above their lowering of BP. However, these data will require the support of other studies before they can be incorporated into the various consensus guidelines.

Reference:

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comparing to decreases of 22% in migraine prophylaxis obtained with lisinopril, 44% with verapamil and 44% with beta-blockers. However, shortcomings of this meta-analysis were that headache was not the primary outcome in any of the individual studies, doses of the ARBs were not standardized, and the types of headaches and their relative frequencies were not specified.

Tronvik et al investigated the use of candesartan (16 mg) for migraine prophylaxis in 60 patients over a 12-week period. They found that the number of days with headache was significantly reduced by 28% (13.6 days with candesartan vs. 18.5 days with placebo) on an intention-to-treat basis. Headache severity and usage of analgesics and triptans were also decreased. Owada also reported eight cases from Japan in which treatment with candesartan reduced the incidence and severity of headache in hypertensive migraineurs.

There is no comparative efficacy data available for either the ARBs or ACE inhibitors in migraine prophylaxis. It is tempting to speculate that drugs that readily cross the blood-brain barrier, such as candesartan, might be more effective in this regard.

Summary
It is generally accepted that severe hypertension, particularly if of acute onset, is a cause of headache. However, uncertainty remains as to whether stage I and/or II hypertension can be regarded as a cause of headache. A recent literature review found that the use of different antihypertensive drugs reduced headaches in hypertensive patients by about one third.

The association between hypertension and the primary headache disorders is also unclear, although several classes of antihypertensive drugs, most recently the ACE inhibitors and ARBs, have been shown to reduce the frequency and severity of migraine headaches. Further studies are required to enhance our understanding of the epidemiology and treatment of headache in the hypertensive population.

References:

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quently done except in specialists’ offices. Time limitations, variable skills and reluctance to dilate the pupils are considerations, but even if early changes (Group A) are difficult to detect or not obvious, valuable information will be missed if hemorrhages, exudates and papilledema are overlooked. Dodson’s Grade A and B classifications cover the elements (but what will happen to “AV nicking”?) and has the merit of simplicity. Whether “normal” findings with the ophthalmoscope—as well as absence of other TOD—will remain reliable and reproducible features of patients labelled as white-coat hypertensives remains to be confirmed.

References:

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