Why Do Treated Hypertensives Suffer Strokes? An Internist's Perspective

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Despite widespread treatment of hypertension, stroke continues to be the third leading cause of death in the United States. Antihypertensive therapy is more effective in preventing hemorrhagic strokes than ischemic strokes. In order to understand the reasons why antihypertensive therapy is only partially successful in the eradication of ischemic strokes, differences in the pathogenesis and treatment of subtypes of stroke must be considered. There are three main stroke subtypes of ischemic strokes: small-vessel arteriopathic (lacunar), large-artery atherothrombotic, and cardioembolic. Hypertension is the major cause of lacunar strokes but plays a lesser role in the pathogenesis of atherothrombotic strokes. Antihypertensive therapy prevents the majority of lacunar strokes but may not have a major impact on the occurrence of atherothrombotic strokes. Due to impaired cerebral autoregulation, overtreatment of hypertension, especially in the elderly and in patients with previous strokes, may paradoxically lead to stroke (J-curve). Assuming that the majority of lacunar strokes are prevented by judicious antihypertensive therapy, future therapeutic efforts should concentrate on the prevention of atherothrombotic and cardioembolic strokes. In this regard, refinement of surgical techniques, pharmacologic approaches aimed at plaque stabilization, and the application of transesophageal echocardiography for the diagnosis of embolic strokes (and anticoagulation for a probable source) are promising. Besides the obvious reasons of noncompliance and inadequate therapy, overly aggressive treatment of hypertension in the elderly and stroke mechanisms unrelated to blood pressure may explain the occurrence of strokes despite our efforts to treat hypertension. (J Clin Hypertens. 2002;4:338–344) ©2002 Le Jacq Communications, Inc.

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Permanent disability due to stroke is the most important complication of hypertension. Yet, our thinking about stroke and its relationship to hypertension is often simplistic, if not unscientific. To paraphrase Gertrude Stein, we seem to think that "a stroke is a stroke is a stroke," and hypertension is its only cause. Stroke is also treated as one disease by the majority of large population surveys and therapeutic intervention trials.[1–3] The main reason for this view has been the difficulty in distinguishing strokes of different etiologies on clinical grounds alone. The availability of modern imaging techniques improved our ability to distinguish among subtypes of ischemic stroke, but despite their application, "cryptogenic" strokes, that is, strokes of undetermined etiology, constitute about 25% of all consecutive cases.[4] The etiologic diagnosis of strokes is further complicated by the presence of two or more potential pathogenetic mechanisms in the same patient.[5] Antihypertensive therapy helps to prevent the majority of hemorrhagic strokes but is less effective in the prevention of ischemic strokes.[6] Stroke continues to be the third leading cause of death in this country.[7] The stroke incidence, which declined in the 1970s and the early 1980s, has remained relatively unchanged during the past 10 years.[7] Antihypertensive therapy is more effective in the primary than in the secondary prevention of strokes,[1,8] suggesting that pathogenetic mechanisms other than hypertension play a role in stroke recurrence.

With refinements in diagnostic techniques, it is time to re-examine the relationship of hypertension to the different types of stroke and the efficacy of antihypertensive therapy in their primary and secondary prevention. The analysis of stroke and

hypertension is confined to ischemic strokes because hemorrhagic stroke is uncommon among treated hypertensives (about 10%) and is strongly related to uncontrolled (neglected) hypertension.[6,9] A better understanding of strokes will inevitably lead to better treatment of patients.

STROKE SUBTYPES

The general internist, and that includes the hypertensionologist, should be able to recognize three subtypes of ischemic stroke, listed in the Table.[10,11] Stroke due to small-vessel arteriopathy (lacunar stroke) may be diagnosed on clinical grounds by the simple circumstance that the patient does not have impairment of cortical functions (vision, language, thought processes, emotions). The neurologic deficit is usually pure motor or sensory loss involving one side of the body. Computed tomographic or magnetic resonance imaging of lacunar strokes reveals a subcortical or brainstem lesion less than 1.5 cm in diameter.

Large-artery atherothrombotic stroke is frequently preceded by ipsilateral transient ischemic attacks (TIAs) and may be stepwise or progressive in onset. In addition to sensory and motor loss of variable severity and distribution, there may also be disturbance of language, vision, or consciousness. On computed tomography and magnetic resonance imaging, there is infarction greater than 1.5 cm in diameter in the cortex or subcortex or both, in the brainstem, or in the cerebellum. For the diagnosis of atherothrombotic stroke, Doppler ultrasonography or angiography must show greater than 50% stenosis of a relevant large extra- or intracranial cerebral artery.

Stroke due to cardioembolism usually occurs suddenly, without prior TIA. Consciousness is more often impaired at onset, and a seizure may occur. The variable clinical deficits and the findings of imaging studies are similar to those of atherothrombotic stroke. The presence of a hemorrhagic component, or involvement of several arterial territories, favors the diagnosis of embolism. A cardioembolic source must be identified. This should be a high-probability source, such as atrial fibrillation, recent anterior wall myocardial infarction (MI), and a mechanical or infected heart valve.

Despite efforts aimed at an etiologic diagnosis, there is a large category of strokes, about 25% of all strokes, the cause of which remains uncertain.[4] Clinically, these strokes are indistinguishable from those due to atherothrombotic disease or cardioembolism, but imaging studies fail to reveal stenosis of a relevant artery or a cardiac source. In 10%–20% of cases, especially in the elderly with risk factors for atherosclerosis, more than one potential cause of stroke may be found.[5] Serial testing may improve diagnostic accuracy. Stroke diagnosis is complicated further by the observation that the etiology of a recurrent stroke may differ from that of the initial stroke.[12] The difficulties encountered in the etiologic diagnosis of stroke, however, must not lead to diagnostic nihilism, because treatment outcome depends on precise diagnosis.

PATHOPHYSIOLOGIC CONSIDERATIONS

Next to aging, hypertension is the most important predisposing condition for stroke,[1,13] but its relative

Table. Stroke Subtypes

Small vessel arteriopathic (lacunar)	
Clinical	Pure sensory and/or motor hemiparesis; clumsy-hand dysarthria syndrome; cortical functions* intact
Diagnosis	CT (MRI) evidence of subcortical hypodense area (<1.5 cm); little or no evidence of large-artery disease or cardioembolism
Large artery atherothrombotic	
Clinical	Recent ipsilateral TIAs, stepwise onset; "stroke syndrome," usually with some impaired cortical functions
Diagnosis	CT (MRI) evidence of infarction (>1.5 cm); relevant large-artery atheromata (>50% stenosis) by Doppler US; little or no evidence for cardioembolism
Cardioembolic	
Clinical	"Stroke syndrome" with some impaired cortical functions of sudden onset
Diagnosis	CT (MRI) evidence of infarction (>1.5 cm); multiple sites; heart disease with recognized source of embolism by transthoracic or transesophageal echocardiography; little or no evidence of large-artery disease
Uncertain/cryptogenic	
Clinical	"Stroke syndrome" with some impaired cortical function
Diagnosis	CT (MRI) evidence of infarction (>1.5 cm); little or no evidence of large artery disease or cardioembolism

CT=computed tomography; MRI=magnetic resonance imaging; TIA=transient ischemic attack; US=ultrasonography
*Cortical functions: vision, language, and cognition

contribution to the three stroke subtypes is not known. The reasons for this are the uncertainties in the diagnosis of stroke subtypes and the difficulties inherent in establishing the duration and severity of hypertension prior to stroke. The limited data that are available indicate that 90% of patients with lacunar stroke have had hypertension, but no more than 50% of patients with atherothrombotic stroke carried the diagnosis of hypertension at the time of stroke occurrence.[14] In the middle-aged, diastolic hypertension is the primary risk factor for lacunar strokes.[15,16] In the elderly, atherothrombotic stroke is more closely linked to systolic blood pressure than to diastolic blood pressure, pulse pressure, or mean arterial pressure.[1] Overall, stroke mortality is predicted by mean blood pressure but not by pulse pressure.[17–19] It is estimated that about 30% of strokes occur in previously normotensive individuals,[11,15,16] but whether these are predominately atherothrombotic or lacunar strokes is not known. The contribution of hypertension to cardioembolic stroke, to our knowledge, has not been quantitated but may be substantial because hypertension is a contributing factor for a number of cardiac conditions that may result in embolization (e.g., atrial fibrillation, MI, congestive heart failure).

The histopathology of typical lacunar and atherothrombotic strokes is sufficiently different to suggest an entirely different pathogenesis. The former is a disease of the media of small arteries, the latter a disease of the intima of large arteries.[20,21] Sclerosis of the media, seen in association with lacunes, is expected to lead to "stiffness," that is, reduced distensibility of the blood vessel; atheroma, on the other hand, may lead to plaque formation, thrombogenesis, and thrombosis (plaque rupture). These differences in histopathology and pathogenesis of the two conditions are reflected in their clinical presentations.

Small-Vessel Arteriopathy (Lacunes) and Cerebrovascular Autoregulation

In the majority of cases, the pathologic basis of lacunar strokes is lipohyalinosis with or without microaneurysm formation of a small artery (40–160 μm outer diameter) or microatheromatous involvement of a penetrating artery (400–500 μm outer diameter) in the brainstem or diencephalon (basal ganglia, internal capsules, thalamus) region.[1,20,22,23] Lipohyalinosis, also referred to as arteriolosclerosis, is degeneration of the media of small arteries with replacement of vascular muscle by lipid deposits and collagen (sclerosis) and loss of structural integrity of the vessel wall. Small arteries of the brainstem are especially vulnerable to surges of blood pressure because autoregulation of blood flow in this region occurs to a lesser extent than in the rest of the brain.[24] The thin media and paucity of elastic tissue in the small arteries of the brainstem and the relative lack of sympathetic innervation may also contribute to the pathogenesis of lipohyalinosis.[25] Once the integrity of the vessel wall is breached, intravascular thrombosis may occur, or a microaneurysm may rupture.

The relative inability of the brain stem circulation to autoregulate intravascular pressure and flow may be compounded by the presence of chronic hypertension. Impairment of cerebrovascular autoregulation occurs relatively early in hypertension and has been well documented in patients with severe, long-standing hypertension.[26–28] It is due in part to reduced capability of cerebral vessels to adapt to functional changes.[28] Cerebrovascular autoregulation is also impaired in diabetes with microangiopathy, which may partly explain the predisposition of diabetic patients to stroke.[29] Further investigation of the relationship between cerebrovascular autoregulation and lacunar strokes is one of the great challenges of research in this field.

Stroke and impaired cerebrovascular autoregulation may be linked in several clinical settings, including aging, aggressive treatment of severe hypertension, and secondary prevention of stroke. That cerebrovascular autoregulation is impaired in the elderly, irrespective of blood pressure status, is known.[30–32] Combined with baroreceptor dysfunction, impaired autoregulation may lead to cerebral hypoperfusion during sleep and in the postprandial period, when blood pressure normally falls.[31] There are disturbing reports of the association of nocturnal and postprandial hypotension and the presence of lacunes in the elderly.[33,34] The association is much more common in previously hypertensive than in normotensive subjects, especially in patients with isolated systolic hypertension.[33,35] Large artery stiffness, the pathophysiologic basis of isolated systolic hypertension, may thus be associated with sclerosis or stiffness of small cerebral arteries, which gives rise to lacunes. Increased arterial stiffness may also explain impaired baroreceptor function in the elderly,[36] completing the vicious circle of episodic hypotension, impaired cerebrovascular autoregulation, and silent strokes.

Aggressive treatment of hypertension may increase the frequency of episodic hypotension in the elderly and lead to paradoxical strokes. The development of stroke in patients with long-standing, severe hypertension shortly after the initiation or escalation of antihypertensive therapy is well known.[37] The use of sublingual nifedipine for the treatment of hypertension has been abandoned because of the occur-

rence of MIs and TIAs and strokes during sudden reduction of blood pressure.[38] In the Systolic Hypertension in the Elderly Program (SHEP), which demonstrated an overall benefit of antihypertensive therapy in the prevention of strokes,[2] lowering of diastolic blood pressure to less than 60 mm Hg was associated with a paradoxical increase of cardiovascular events (J-curve), including strokes, in the treated group of subjects.[39] Spontaneously low diastolic blood pressures in the placebo group, on the other hand, were not associated with excess cardiovascular morbidity. Despite the increase in the cardiovascular event rate at low diastolic blood pressures, the stroke incidence of treated subjects was not greater than that of placebo-treated subjects.

The first study that clearly showed a J-shaped relationship between diastolic blood pressures and the incidence of stroke in treated hypertensive subjects is the recently published Rotterdam Study from The Netherlands, a prospective, population-based cohort study.[40] As in the reanalysis of the SHEP data, the inflection point between treatment benefits and risks of overtreatment occurred at less than 65 mm Hg diastolic blood pressure. The average blood pressure of treated hypertensive patients in this trial was 157/80 mm Hg. From the published data, it is not clear whether the low diastolic blood pressures were induced by antihypertensive therapy or were due to complicating cardiovascular disease. While a J-curve relationship between treated diastolic blood pressures and the rate of cardiovascular events exists, it is rare. Its rarity may be due to the wide margin of safety in the delivery and utilization of oxygen by the brain; oxygen saturation of jugular venous blood at rest is about 60%–70%, compared to 30% in coronary sinus blood.[27]

Secondary prevention of stroke by antihypertensive therapy has been disappointing. Stroke recurrence rates in Rochester, MN remained stable in the 1960s and 1970s, in contrast to the decline in the incidence of initial strokes during the same period.[8] A 3-year secondary prevention trial conducted in the 1970s that involved 452 patients with moderate hypertension and a recent history of stroke or TIA did not demonstrate a benefit of antihypertensive therapy.[41] Eighty percent of participants in this trial were African Americans. At the end of the trial, the average blood pressures of participants on active or placebo treatment were 138/87 and 168/98 mm Hg, respectively. Stroke recurrence was unrelated or weakly related to the level of blood pressure at baseline and during treatment. In another secondary prevention trial, a J-curve relationship was observed between treated diastolic blood pressure (but not systolic blood pressure) and the recurrence of lacunar strokes in 368 hypertensive patients during the first 5 months after the initial stroke.[42] The paradoxical increase in stroke incidence occurred with treated diastolic blood pressures less than 80 mm Hg. It was also reported that the incidence of recurrent strokes, predominantly lacunar in type, was higher during antihypertensive therapy in patients with nocturnal episodes of hypotension than in patients who maintained normal blood pressure during sleep.[43] Fortunately, this relationship between overly aggressive antihypertensive therapy and stroke recurrence disappears after 1–2 years of treatment.[44] This may relate to the long-term improvement of cerebrovascular autoregulation with effective antihypertensive therapy.[26,28] Finally, a recent meta-analysis of secondary stroke prevention by antihypertensive therapy reported a 28% risk reduction.[45] The analysis has some limitations. Among others, it included participants from primary prevention trials who had a remote history of stroke, and the results of a large Chinese secondary prevention trial that did not discriminate between normotensive and hypertensive participants.

Atherothrombosis and Arterial Stiffness

The pathogenesis of atheroma formation and the contribution of hypertension to it are poorly understood.[1] The common denominator appears to be age- and hypertension-related stiffening of conduit arteries, but the way in which increased stiffness leads to endothelial damage and atheroma formation is not clear. In the Framingham cohort, systolic blood pressure, a marker of large artery distensibility, was more closely linked, in a positive fashion, to the occurrence of atherothrombotic strokes than was diastolic blood pressure.[1] However, the association between arterial stiffness and atheroma formation is not a strong one. Nor is hypertension a major contributor to atheroma formation. Blood pressure control has no major impact on the progression of systemic atherosclerosis.[46] The importance of hypertension may lie in the pathogenesis of atheroma-related complications, namely, plaque rupture, thrombogenesis, and artery-to-artery embolus.[47]

As in the case of lacunar infarcts, excessive lowering of diastolic blood pressure in the presence of major cerebral artery occlusion or severe stenosis may result in cerebral ischemia. Repetitive, stereotypical TIAs were observed in elderly patients with orthostatic hypotension due to excessive lowering of blood pressure with antihypertensive medications, or to autonomic nervous system impairment in diabetics who also had severe stenosis of extracranial arteries; treatment of orthostatic hypotension relieved the symptoms.[48] A J-shaped relationship exists not only

between diastolic blood pressure and the rate of recurrence of lacunar strokes (see above) but also between diastolic blood pressure and the rate of recurrence of atherothrombotic strokes, suggesting that hemodynamic factors may contribute to stroke recurrence.[42]

Cardioemboli

Emboli of cardiac origin can be composed predominately of white or red platelet thrombi, fibrin (ventricular aneurysm), calcific material (aortic stenosis), bacteria, or tumor (myxoma).[49] The risk of embolization varies, depending on the source and the clinical setting. The annual incidence of embolic strokes for patients with nonrheumatic atrial fibrillation varies from about 3% for patients younger than 60 to 5% for patients older than 70.[49] For patients within 2–4 weeks of an acute MI, the risk of embolization is about 1% for inferior wall MI and about 6% for anterior wall MI.[49] For a patient with an acute anterior wall MI and a demonstrated left ventricular thrombus, the risk of embolization within the first month after the event may be as high as 10%.[49] Little is known about the role of hypertension in the pathogenesis of cardioembolic strokes. While hypertension is a risk factor for atrial fibrillation and MI, it is not known whether an already existing atrial or intraventricular thrombus is more likely to be mobilized in a hypertensive or in a normotensive patient.

THERAPEUTIC IMPLICATIONS

The importance of a pathogenetic diagnosis of stroke cannot be overemphasized. Pathogenetic diagnosis is especially important in the secondary prevention of strokes because antihypertensive therapy in this situation is less effective and in some cases may be harmful. In this regard, the present review is a repetition and elaboration of Spence's appeal that appeared in 1986.[47] In it, he argued and provided preliminary supporting data that antihypertensive therapy prevented the large majority of lacunar strokes but not those due to atherothrombotic disease, an important distinction for both therapeutic and investigational purposes. Analysis of the types of stroke in the SHEP trial (discussed previously) revealed that antihypertensive therapy reduced the relative risk of lacunar strokes by 47% but had no effect on the rate of occurrence of atherothrombotic strokes.[9] However, there were few atherothrombotic strokes diagnosed in the study, and close to 50% of strokes were of uncertain pathogenesis. Assuming that the large majority of lacunar strokes are prevented by customary antihypertensive therapy, more aggressive treatment for either primary or secondary prevention purposes may not be justified, considering that overtreatment itself may be occasionally harmful (see above). The results of the recently concluded Hypertension Optimal Treatment (HOT) trial support this view[50]; lowering of diastolic blood pressure below 80 mm Hg did not provide additional benefit in the prevention of cardiovascular complications, including stroke, compared to reduction of diastolic blood pressure to 85 mm Hg, except in diabetic patients, who benefited from having their diastolic blood pressure lowered to less than 80 mm Hg. This clinical experience in nondiabetic patients is different from epidemiologic data based on population surveys of normotensive and hypertensive subjects, which show that the lower the baseline diastolic blood pressure, including values well below 80 mm Hg, the less likely that a stroke will occur[51]; epidemiology cannot be translated directly into therapeutics.

The management of hypertensive patients with atherothrombotic stroke differs in important ways from that of patients with pure lacunar stroke. The majority of these patients are elderly, with more than one—and sometimes multiple—potential risk factors for stroke.[5] The emphasis should be on the prevention of recurrent artery-to-artery embolization, either by surgical removal of the source of emboli,[52] if this is possible, or by antiplatelet therapy.[53] Antihypertensive therapy in the secondary prevention of atherothrombotic strokes is of unproved benefit.[9,50] Slowing the progression of atheromatous disease by lipid-lowering therapy and plaque stabilization by pharmacologic means are under investigation.[54,55]

The key to therapy of cardioembolic strokes is diagnosis.[16] Transesophageal echocardiography has been advocated in all patients with stroke and normal sinus rhythm whose stroke mechanism is unclear. This approach is of potential benefit to young and middle-aged patients. In the elderly, the frequent occurrence of more than one potential risk condition for stroke limits the diagnostic usefulness of transesophageal echocardiography.[5]

FUTURE DIRECTIONS

In this brief review, I have pointed out some of the gaps in our knowledge about the role of hypertension in the pathogenesis of stroke subtypes and the effectiveness of antihypertensive therapy in their prevention and treatment. Much of what we know comes from large-scale surveys and therapeutic trials. While these studies have been useful in defining the risk factors for stroke in general and in demonstrating the overall benefits of antihypertensive therapy, they are inadequate for detecting differences in the pathogenesis and treatment of subtypes of stroke. For that, smaller-scale surveys and trials that clearly identify the type of stroke that subjects have had are needed. Risk factors need to be defined for clearcut,

isolated lacunar, atherothrombotic, and cardioembolic strokes. For instance, what is the incidence of pre-existing hypertension in patients who have suffered their first lacunar or atherothrombotic stroke? What are the contributions of age, gender, cholesterol levels, diabetes, smoking, and so forth to lacunar strokes compared to atherothrombotic strokes? Are hypertensive patients with atrial fibrillation more likely to suffer a stroke than normotensive patients with the same condition? When it comes to secondary prevention, how effective, relatively, is antihypertensive therapy in patients with previous lacunar, atherothrombotic, or cardioembolic stroke? How aggressive should antihypertensive therapy for each of these conditions be? On the pathophysiologic level, does impaired autoregulation of blood flow to the midline structures of the brain play a role in the development of lacunar strokes, and is atheromatous plaque stability or instability, once we can measure this, a determining factor in the occurrence of atherothrombotic strokes? The answers to these and similar questions will depend on our ability to clearly identify patients with subtypes of stroke and to follow them long-term.

In summary, besides the obvious reasons of noncompliance and inadequate therapy, treated hypertensive patients may suffer strokes because excessive lowering of blood pressure itself may lead to stroke; strokes may occur in the absence of hypertension, and hypertension is only a predisposing condition for, not the cause of, atherothrombotic and cardioembolic strokes.

Better understanding of the pathology and pathophysiology of stroke subtypes is needed to improve diagnostic precision and to prevent strokes not directly related to hypertension.

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