Chapter 6
Pathophysiology and Mechanisms Whereby Hypertension May Cause Stroke

Beom Joon Kim, Hee-Joon Bae, and Lawrence K.S. Wong

The association between hypertension and stroke has been known since the nineteenth century. Although a number of vascular risk factors have been identified since, it is estimated that 51 % of stroke death may be attributable to elevated systolic blood pressure. The powerful effect of hypertension on the incidence and mortality of stroke has repeatedly been documented regardless of region or ethnic background [1].

Hypertension is the most important modifiable risk factor for stroke. The prevalence of hypertension in ischemic stroke patients ranges from two-thirds to as much as 80 % [2]. The degree of elevation of blood pressure is tightly correlated with the risk of stroke. The risk curve is a continuum without any clear point separating the stroke-prone from the non-stroke-prone subjects [3–5]. Hypertension plays a key role in the pathogenesis of large artery atherosclerosis, which in turn causes ischemic stroke due to thrombotic arterial occlusion, artery-to-artery embolism, or a combination of these factors. In the microscopic level of small arteries or arterioles, hypertension also generates specific vasculopathies such as lipohyalinosis and thus causing lacunar infarctions. Hypertension does not seem to directly cause cardioembolic stroke through generation of intracardiac thrombus, but such thrombophilic cardiac conditions including atrial fibrillation or ischemic cardiomyopathy are strongly under the influence of chronically elevated blood pressure. Additionally, hypertension is a major risk factor for intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH), two major subtypes of hemorrhagic stroke.

B.J. Kim, M.D., Ph.D. • H.-J. Bae, M.D., Ph.D. (✉)
Department of Neurology, Seoul National University Bundang Hospital, Gyeonggi-do, South Korea
e-mail: braindoc@snu.ac.kr

L.K.S. Wong, M.D.
Departments of Medicine and Therapeutics, Chinese University of Hong Kong, Hong Kong Special Administrative Region, Hong Kong, China

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Microscopic and biological mechanisms contributed by hypertension on the cerebral vasculature will be discussed in other chapters. In this chapter, we will discuss clinical issues related to chronically elevated blood pressure in relation to ischemic or hemorrhagic strokes.

Mechanisms of Ischemic Stroke or Tia in Relation to Hypertension

Large Artery Disease

Artherosclerotic Stroke

Atherosclerosis may involve multiple arteries throughout the body, including the aorta, coronary arteries, peripheral blood vessels, and cerebral blood vessels. Fatty streaks, fibrous plaques, and complicated plaques are the pathologic hallmarks of atherosclerosis. Atherosclerotic lesions begin with an inflammatory reaction followed by smooth muscle proliferation and thickening of the arterial wall. Hypertension, endothelial dysfunction, shear stress, elevated low-density lipoproteins, free radicals, and chronic inflammatory response are closely associated with the process of atherosclerosis [6]. The common locations of atherosclerosis include the bifurcation of the common carotid artery, origin and intracavernous portion of the internal carotid artery (ICA), first segment of the middle cerebral artery (MCA), origin and the distal portion of the vertebral artery, and mid-portion of the basilar artery. Vulnerable plaques in the coronary artery tend to have a thin fibrous cap and a large lipid core. Autopsy findings and histopathological examination of surgical endarterectomy specimens suggest that intraplaque hemorrhage, reparative neovascularization, and ulceration are the factors leading to plaque instability in the carotid artery [7–9]. Atherosclerosis of the MCA most commonly affects the M1 segment, which extends from the origin of the artery to the insula. The lenticulostriate arteries arise from this section, and the origins of these vessels can be affected by the development of atherosclerotic plaque, which may result in an isolated small subcortical infarct. Hemorrhage, ulceration, and calcification are less common in intracranial atherosclerotic plaques compared to extracranial plaques. An autopsy study from Hong Kong found that luminal stenosis caused by atherosclerotic plaque, percentage of lipid in the lesions, and the presence of intraplaque neovasculature in the MCA are independent risk factors for MCA infarcts [10].

Recent development of imaging modalities including high-resolution MRI, enhanced doppler technology, and the combination of PET-MRI scans provide deeper insights into the characteristics of atherosclerotic plaques. Atherosclerotic plaques are largely divided into stable or vulnerable plaques, and the former usually grow slowly and thus causing hemodynamic insufficiency of the perfused territory due to intraluminal narrowing. However, the vulnerable plaques, characterized by thin fibrous cap over the necrotic core with high density of inflammation, have

a tendency to rupture and cause sudden formation of intraluminal thrombus with distal embolization or vascular occlusions in situ [11].

Age, hypertension, diabetes mellitus, smoking, and hyperlipidemia are well-known risk factors for atherosclerosis. Large artery atherosclerosis is the most common type of vascular pathology, in which fibrous and muscular tissues proliferate in the subintima of the vessel wall, and fatty materials form plaques that can impinge on the vessel lumen. Platelets then adhere to plaque and form clumps that serve as a nidus for the deposition of fibrin, thrombi, and clot [12]. Acute thrombosis begins with fissuring of the fibrous cap of the atherosclerotic plaque, and the release of tissue factors promotes the development of a clot adjacent to the plaque. Local occlusion can then lead to a significant decrease in blood flow and oxygen supply, which may cause ischemic brain damage.

In contrast to Caucasians, intracranial occlusive disease is common in persons of Asian and African ancestry [13–16]. Intracranial atherosclerosis accounts for 33–50 % of stroke in Asians [13], and up to 10 % of stroke or TIA in the USA are caused by intracranial artery stenosis [17]. Age, hypertension, diabetes mellitus, and probably the metabolic syndrome are the most consistent risk factors for intracranial atherosclerosis [18]. And a higher incidence of hypertension in populations of African and Asian ancestry may explain their higher prevalence of intracranial atherosclerosis. Severity of stenosis is widely accepted as the major prognostic risk factor in patients with symptomatic and asymptomatic ICA disease [19, 20], and has been reported to increase the risk of ischemic stroke in the territory of symptomatic intracranial arterial stenosis [21]. Furthermore, progression of MCA occlusion as assessed by an increase of flow velocity on TCD is associated with an increased risk of further cardiovascular events [22].

Peculiarity of Intracranial Artery Atherosclerosis

Intracranial artery stenosis is an interesting topic, which deserves a separate discussion. Asian and African-American patients have disproportionately higher rates of intracranial atherosclerosis than Caucasian populations [23–25]. In a postmortem study from China, severe intracranial atherosclerosis was found in 30 % of subjects in their 60s and 70s and around 50 % in elderly patients aged ≥80. Such ethnic disproportion has not been clearly elaborated but it may originate from differences in genetic background or in the profile of vascular risk factors. Interestingly, South Korea, which has entered into a modern industrialized society within a short time period of 20–30 years, had significant changes in the proportion of intracranial stenosis over extracranial stenosis which supports a role of nutritional and environmental factors [26].

Intracranial atherosclerosis shares basic pathological components with extracranial atherosclerosis; intimal necrosis and proliferative fibrosis of intima and adventitia with extension of vasa vasorum into the vascular media. However, two major characteristics distinguish intracranial and extracranial atherosclerosis; the later onset and the more stable plaque phenotype in intracranial arteries [18].

The above two features may be explained by the distinct characteristics of the intracranial arteries, including (1) thicker, denser internal elastic lamina and no external elastic lamina; (2) vasa vasorum only in large intracranial arteries surrounded by CSF; (3) distinct vessel wall metabolism; (4) presence of tight Junctions between endothelial cells; (5) reduced endothelial permeability; (6) relative insensitivity to sympathomimetic and histamine stimulations compared with systemic vessels; (7) enhanced protective mechanisms against oxidative stress; and (8) flow characteristics determined by circle of Willis anatomy [18]. Thus far, the larger antioxidant response of intracranial compared with extracranial arteries is the single reported functional characteristic that may contribute to the reported later onset and steep increase in intracranial atherosclerosis in the sixth decade.

Clinical issues related to intracranial atherosclerosis may be summarized by the following points: (1) occlusion of small perforator branches in middle cerebral arteries or basilar arteries. Such ischemic stroke from branched artery occlusion may occur long before any noticeable luminal narrowing develops. (2) When the cross-sectional area of intracranial arteries became smaller, hemodynamic insufficiency and related pathological changes may develop before a typical atherosclerotic pathology accumulates. However, it is relatively not uncommon that the extent of any irreversible infarction became relatively smaller due to leptomeningeal collaterals from posterior cerebral arteries or extracarotid arterial channels. (3) Intracranial arteries intermittently pose technical hurdles for endovascular interventions.

Artery-to-Artery Embolism

Artery-to-artery embolism is another important stroke mechanism in patients with extracranial large artery disease. Emboli are composed of clot, platelet clumps, or fragments of plaques that break off from the proximal vessels [27]. Proximal ICA and extracranial vertebral artery atherosclerosis is an important source of embolism. High-intensity transient signals (HITS) recorded over the MCA with TCD monitoring can be used to detect artery-to-artery embolism in patients with proximal artery disease [21].

Artery-to-artery embolism is also an important but less well-recognized mechanism of stroke among patients with intracranial artery disease. Wong et al. [22] reported that among stroke patients with multiple acute infarcts and MCA stenosis, unilateral, deep, chainlike border-zone infarcts were the most common pattern. However, the number of microembolic signals predicted the number of acute infarcts, which suggested an embolic mechanism for this pattern of stroke. A possible explanation is that emboli in the trunk of the MCA may simultaneously occlude several of the lenticulostriate perforating vessels.

Branch Atheromatous Disease

Atheromatous plaque, often referred to as microatheroma, can obstruct the orifices of penetrating arteries and occlude the lumen, causing an isolated small subcortical infarct. Pathological features of microatheroma include microdissection, plaque

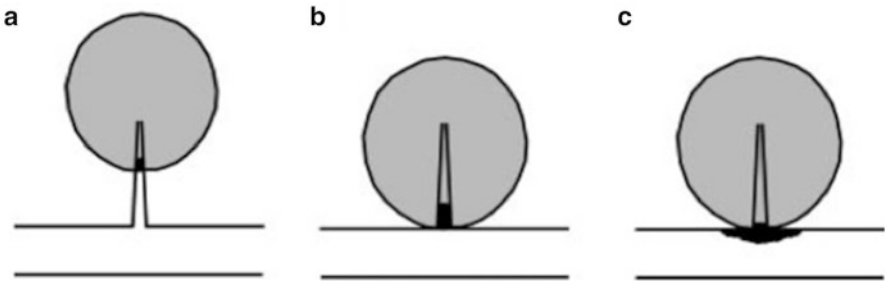

Fig. 6.1 Classification of SSSI according to the lesion extension and the presence of PAD. (**a**) Distal SSSI without PAD; (**b**) proximal SSSI without PAD; (**c**) SSSI associated with PAD. *SSSI* indicates single small subcortical infarction and *PAD* parent artery disease. (From Nah H-W, Kang D-W, Kwon SU, Kim JS. Diversity of Single Small Subcortical Infarctions According to Infarct Location and Parent Artery Disease Analysis of Indicators for Small Vessel Disease and Atherosclerosis. Stroke; a journal of cerebral circulation. 2010;41(12):2822-7, with permission)

hemorrhage, and deposition of platelet-fibrin materials [28]. Branch atheromatous disease was first described in pontine infarction caused by basilar branch occlusion, but its concept can be applied to infarcts in the territory of lenticulostriate branches, thalamogeniculate branches, anterior choroidal artery, Huebner's artery, and thalamoperforating artery branches [29]. This pathogenic mechanism of stroke has been underappreciated in the past [29–31]. However, recent studies have demonstrated that in patients with MCA stenosis, occlusion of a single penetrating artery to produce a small subcortical lacune-like infarct is relatively common [32, 33].

Technological development of MRI permitted the acquisition of high-resolution images on intracranial vascular wall pathologies. Such MRI techniques visualized that a part of intracranial arteries, previously considered as conspicuous but undisturbed vascular lesions, have spread atherosclerotic plaques alongside the curves of vascular lumen and thus occluding the orifice of parenchymal perforators. In this context, detailed classification has been proposed as following [34] (Fig. 6.1). The traditional lacunar infarction pathology, mainly composed of lipohyalinosis and fibrinoid necrosis of microscopic arteriolar walls, may locate at the inside of brain parenchyma thus causing small and confined infarction (Fig. 6.1a). However, atherosclerotic pathologies involving vascular walls of intracranial arteries may involve the opening of direct and long perforators (Fig. 6.1c). Such occlusion may result in a vertically elongated lesion from basal ganglia to corona radiata in the lenticulostriate artery territory or stretched lesion involving basal surface of the pons or midbrain in the brainstem.

Likewise, a recent report supported the concept. The authors classified so-called traditional lacunar infarction with axial diameter less than 1.5 cm into branch atheromatous diseases and lacunar infarctions by involvement of the basal surface of brainstem or elongated lesions in lenticulostriate artery territories. Early neurological deterioration, defined as any new neurological symptom/signs within 3 weeks from the index stroke, occurred more frequently in a group of branch atheromatous disease than in a lacunar infarction group [35].

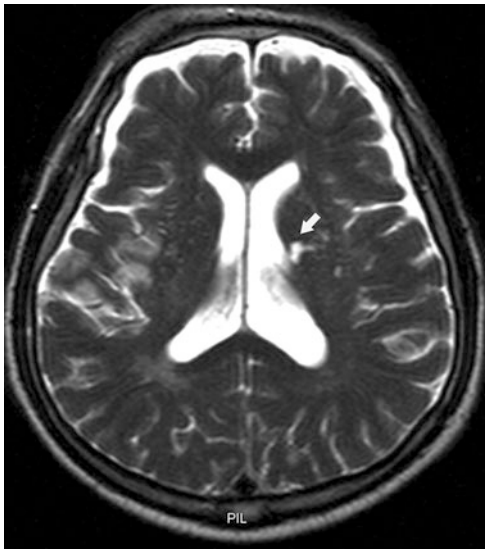

Fig. 6.2 Lacunar infarction. *White arrow* indicates a small lacunar infarction in left corona radiata

Small Vessel Occlusion

The classical example of small vessel disease is the occlusion of a single, non-branching penetrating end artery (usually smaller than 500 μm in diameter), which causes small subcortical lacunar infarcts (1–20 mm in diameter) (Fig. 6.2). There are a number of potential causes of small vessel occlusive disease, e.g., embolism and vasospasm; however, lipohyalinosis and atherosclerosis remain the two major pathologies.

Fibrinoid necrosis is caused by the insudation of plasma proteins, i.e., fibrin, into the arteriolar wall, which is common in hypertensive brains. The affected area is deeply eosinophilic and structureless, or very finely granular (Fig. 6.3). In hypertensive individuals, the vessel wall may also be eosinophilic and structureless due to degeneration of muscle and collagen (hyalinization). Hyalinization is considered as a "mundane" change because it does not cause the rupture of the blood vessels. However, on light microscopy, it may be difficult to distinguish between hyalinization and fibrinoid necrosis. Special stains such as the Putz stain may help in differentiating between fibrinoid and hyaline material [36]. Immunohistochemistry and electron microscopy have established that the fibrinoid areas do indeed contain fibrin, and electron microscopy clearly distinguishes fibrin with its characteristic periodicity from areas of hyalinization which contain only degenerated collagen and smooth muscle and unidentified amorphous material [36, 37]. Fibrinoid deposition may be very segmental so that the material appears only at widely separated points along the length of arterioles or only in a portion of its circumference. In a study combining light microscopy with electron microscopy, fibrinoid necrosis occurred in vessels that also displayed hyalinization with no suggestion that fibrinoid necrosis preceded hyalinization [38].

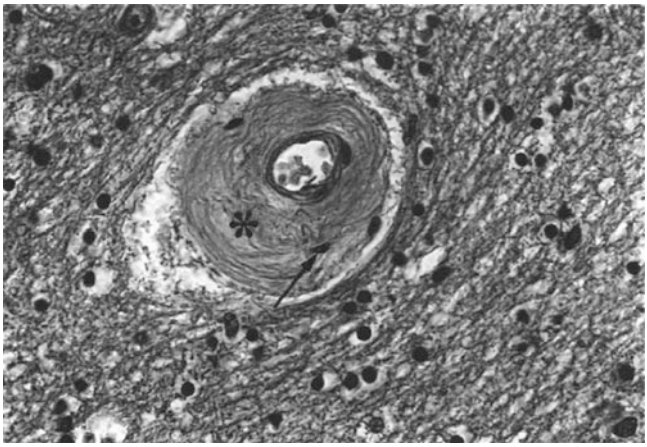

Fig. 6.3 Hyaline arteriosclerosis, roughly concentric vessel wall thickening by hyaline collagenous material (*asterisk*), with occasional surviving smooth muscle cell nuclei (*arrow*). (From Lammie GA. Pathology of small vessel stroke. Br Med Bull. 2000;56:296–306, with permission [39])

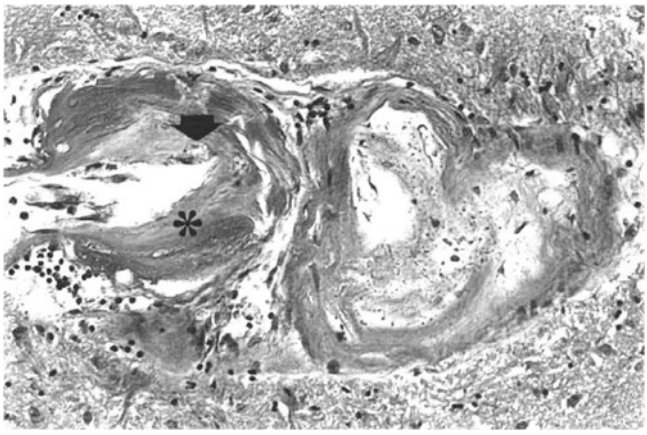

Fig. 6.4 Lipohyalinosis, an asymmetrically thickened, disorganized vessel wall with focal fibrosis (*asterisk*) and foam cell infiltration (*thick arrow*). (From Lammie GA. Pathology of small vessel stroke. Br Med Bull. 2000;56:296–306, with permission.)

Lipohyalinosis, formerly considered the most frequent cause of lacunes, shares some of the histochemical, electron microscopic, and immunofluorescent characteristics of fibrinoid necrosis [40]. Lipohyalinosis has been thought to be an intermediate stage between fibrinoid necrosis of severe hypertension and microatheroma associated with more long standing hypertension. Although often considered identical, lipohyalinosis and fibrinoid necrosis differ histochemically in that fibrinoid necrosis stains strongly for phosphotungstic acid hematoxylin, whereas lipohyalinosis does not (Fig. 6.4) [41, 42]. Lipohyalinosis is found most commonly in a setting of chronic, nonmalignant hypertension, whereas fibrinoid necrosis is said to be

found uncommonly with extreme blood pressure elevation such as those that occur in hypertensive encephalopathy and eclampsia [40]. Original Fisher's description was that vascular lesions involved small arteries of 40–200 μm diameter and caused correspondingly small, often asymptomatic, cerebral infarcts, particularly in the striatocapsule [43, 44]. He chose the term lipohyalinosis instead of fibrinoid necrosis just because he perceived that the affected arteriolar segments also contained lipid. Owing to his huge influence in this area, the term lipohyalinosis has come into widespread use, while fibrinoid necrosis has become the less-used term.

The most common locations for lacunes are the putamen and the pallidum, followed by the pons, thalamus, caudate nucleus, internal capsule, and corona radiate [44]. The incidence of cerebral lacunes has declined since the introduction of antihypertensive therapy, an indication that antihypertensive therapy is effective in the prevention of this type of stroke [44]. Initially, lipohyalinosis was thought to be the main cause of lacunar stroke. However, with recent advances in modern neuroimaging, microatheroma is now thought to be the most common mechanism of small vessel occlusion, especially in Asian populations with high prevalence of large intracranial artery stenosis [45]. The culprit atheromatous plaques are often seen in the proximal portion of the perforating artery (microatheroma), at its origin (junctional atheroma), or in the parent artery itself (mural atheroma). Infarcts are related to stenotic or occlusive plaques, some but not all of which may be complicated by overlying thrombus [44]. Subcortical infarcts caused by atheromatous disease are larger in size, usually more than 5 mm in diameter, and associated with a more unstable clinical course than those caused by lipohyalinosis [45].

Cardioembolism

In cardioembolic stroke, the embolus most commonly originates from the heart valves, endocardium, and atrial or ventricular cavities. Other clots may originate in systematic veins and then travel to the brain through cardiac defects, such as a patent foramen ovale, a process termed paradoxical embolism. A larger infarct is more common in cardioembolic stroke when compared to an artery-to-artery embolic stroke because the clots are larger and there is insufficient time to develop an effective collateral circulation. Atrial fibrillation is the most common cardiac source of brain embolism. Atrial fibrillation is more likely to develop in hypertensive patients with left ventricular hypertrophy and an increased left atrial size. A recent study also showed that regression of left ventricular hypertrophy with antihypertensive therapy reduced the risk of developing atrial fibrillation [46]. Hence, better blood pressure control in addition to anticoagulation may further reduce the risk of embolic stroke.

Hemodynamic Stroke

Cardiac failure and systemic hypotension are the two major causes of systemic hypoperfusion. Systemic hypoperfusion is more generalized than cerebral arterial thrombosis or embolism and usually affects both cerebral hemispheres. Recent

studies have demonstrated an association between blood pressure and heart failure. In a US study of over 48,000 patients admitted with acute heart failure, patients in the lowest quartile of systolic pressure (<120 mmHg) had the highest in-hospital and 3-month postdischarge mortality rate [47]. A prospective community-based study found that nondipping of nocturnal blood pressure conferred an additional risk of developing chronic heart failure beyond conventional blood pressure measurement [48]. Therefore, we speculate that good control of blood pressure may lower the risk of developing cardiac failure and thereby lower the risk of cerebral hypoperfusion.

Additionally, chronic hypertension leads to atherosclerosis and increased peripheral vascular resistance, which may further reduce the collateral reserve and result in severe ischemia distal to an arterial occlusion [49]. The border-zone areas between vascular territories are usually vulnerable to hypoperfusion, and when there is a profound decrease in systemic blood pressure, watershed infarcts occur in these areas.

Hypoperfusion caused by a process occurring at a distance from the brain (i.e., the heart or extracranial arteries) rarely produces major brain infarction. In contrast, decreased blood flow caused by a lesion directly at the site of brain tissue is not so benign. Occlusion of penetrating arteries often causes an infarct in the territory supplied by the obstructed artery. In addition, severe intracranial arterial disease also seems more likely to cause brain infarction than extracranial occlusive disease [50].

Traditionally, hypoperfusion and embolism are considered independent mechanisms of stroke in patients with arterial occlusive disease. Caplan proposed that they often coexist in patients with severe occlusive disease [51, 52]. Arterial luminal narrowing and endothelial abnormalities promote clot formation and subsequent embolization, whereas reduced perfusion limits clearance of emboli, especially in the border zones. Impaired washout is an important mechanism that combines hypoperfusion, embolization, and brain infarction [51, 52].

Stroke and the Variability of Blood Pressure

Blood pressure tends to fluctuate over time. Such variability is thought to reflect normal physiology of the autonomic nervous system, cardiac cycle and changes in body posture as well as external environmental change, psychological stress and circadian rhythm [53].

Short-term variability of blood pressure, usually referring to beat-to-beat variability over the 24 h of a single circadian cycle, represents an adaptive response of body regulatory systems to the internal and external environment. Short-term variability is usually summarized as an average of standard deviation or a coefficient of variation but is only modestly associated with cardiovascular complications [54, 55]. Long-term variability usually refers to the variation of blood pressure readings between clinic visits, over seasons and years. Surprisingly, long-term blood pressure variability shows only a weak correlation with short-term fluctuations and may be affected by environmental changes between each measurement and the exposure to BP-lowering medications [56–58].

Until recently published pivotal papers, fluctuations in blood pressure were mostly dismissed and not included in analyses. However, a series of papers published in 2010 demonstrated that such variability is important and may influence certain vascular outcomes after stroke, for example, and certain classes of blood pressure lowering medication may modify blood pressure variability better than other classes of blood pressure lowering medication. Rothwell and colleagues selected recent ischemic stroke or transient ischemic attack patients with more than seven measurements of office blood pressure over at least a 4-month interval. They discovered there is a significant variation in the blood pressure readings over the long period of follow-up, and the blood pressure variability showed noticeable correlation with recurrent stroke events [59]. In a parallel paper, they reported that visit-to-visit variability was more evident in a beta-blocker treated group than in a calcium channel blocker treated group. This suggested that blood pressure variability itself may be mitigated [56].

Earlier, Swedish investigators documented that blood pressure lowering medication may protect against stroke by lowering variability of blood pressure as well as by decreasing the level of blood pressure [60]. In a large cohort of 16,000 hypertensive patients with a follow-up duration up to 35 years, the investigators detect a consistent association between long-term blood pressure variability and the risk of cardiovascular diseases and vascular mortality [61]. Diaz and colleagues reported a meta-analysis of seven cohort studies and noted that for each 5 mmHg higher standard deviation of systolic blood pressure, the risk of cardiovascular diseases were increased by 17 % for stroke, by 27 % for coronary heart disease, by 12 % for all cardiovascular diseases, and by 22 % for all-cause mortality [62]. The strength of association was moderate, and detailed indices of BP variability were not analyzed.

Mechanisms of Intracranial Hemorrhages in Relation to Hypertension

Intracranial hemorrhages involve the brain parenchyma or subarachnoid space, or both. Approximately 15 % of strokes are hemorrhagic. While this accounts for a small proportion of stroke, hemorrhagic stroke has a higher mortality rate compared to ischemic stroke. Hypertension and ruptured cerebral aneurysms are two major causes of intracranial hemorrhage, which are discussed subsequently.

Hypertensive Intracerebral Hemorrhage

Traditionally, hypertension has been considered the predominant cause of ICH [63]. Hypertension-related ICH often leads to subcortical hemorrhage, such as in the putamen (Fig. 6.5) and adjacent internal capsule, thalamus, pons, and cerebellum. However, the importance of hypertension in the etiology of lobar hemorrhage should also be recognized. A study by Broderick and colleagues found that

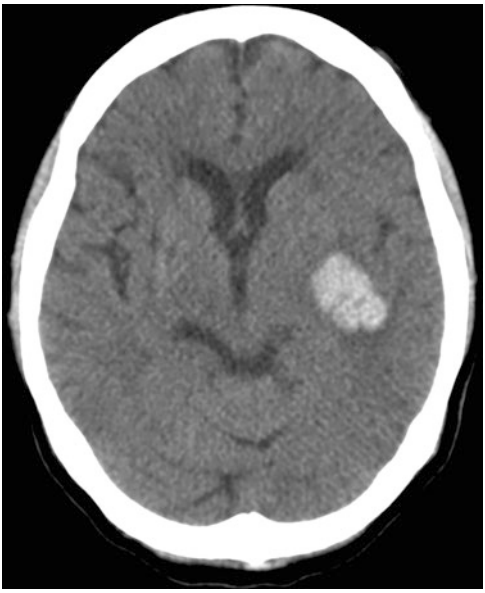

Fig. 6.5 Intracerebral hemorrhage. A small hypertensive intracerebral hemorrhage in *left* basal ganglia

hypertension is nearly as common in primary lobar hemorrhage as in deep hemispheric, cerebellar, and pontine hemorrhages, and its association with lobar hemorrhage does not diminish with advancing age [64]. In this study, 67 % of 66 patients with lobar ICH had hypertension, compared to 77 patients with deep hemispheric (73 %), 11 with cerebellar (73 %), and 9 with pontine (78 %) hemorrhages.

There are two important mechanisms that result in hypertensive ICH: (a) rupture of small penetrating arteries damaged by chronic hypertension and aging and (b) acute elevation of blood pressure leading to rupture of normal arterioles and capillaries.

Chronic Hypertension

Chronic hypertension produces arteriolar changes consisting of fibrinoid necrosis, lipohyalinosis, medial degeneration, and microaneurysm formation, all of which make the vessel susceptible to rupture. The rupture usually occurs in the middle or distal portions of penetrating arteries at or very near to bifurcations. The role of microaneurysms in causing ICH was first proposed by Charcot and Bouchard in 1868, but has been debated over a century. There is accumulating evidence against the theory that the spontaneous ICH is due to a rupture of Charcot–Bouchard microaneurysms as it has never been clearly identified as the definite cause of spontaneous cerebral hematomas. Challa et al. [65] failed to demonstrate microaneurysms in hypertensive patients with spontaneous ICH. An electron microscopic study of ruptured arteries in hypertensive ICH showed severe degenerative changes in 46 of 48 ruptured arteries, but ruptured microaneurysms were found only in two cases [66]. These studies indicated that degenerative changes caused by age and hypertension can predispose to ICH, but it is not certain that a ruptured microaneurysm is the cause of the bleeding.

Acute Hypertension

In clinical practice, many patients with ICH have no prior history of hypertension. In addition, pathologic evidence of chronic hypertension, such as left ventricular hypertrophy or other cardiac and renal changes, is often not found. Bahemuka et al. [67] found only 46 % of fatal cases of spontaneous ICH had chronic hypertension or left ventricular hypertrophy. Similarly, in a case series of 154 patients with spontaneous ICH during 1 year, only 45 % had a history of hypertension [68]. In these two studies, the location of hematoma, increased blood pressure on admission, and absence of other etiologies suggest that the ICH is often caused by an acute elevation of blood pressure. Evidence also indicates that an acute increase in blood pressure and blood flow can precipitate rupture of normal arterioles and capillaries unprotected from these changes in the absence of prior hypertension. Usually, the more sudden and the more severe the change, the higher the risk of rupture.

The combination of a significant increase in cerebral blood flow and blood pressure may also lead to ICH following carotid endarterectomy or carotid artery stenting. A retrospective review of 4494 patients who underwent carotid endarterectomy or carotid artery stenting found that strict control of postoperative blood pressure prevents ICH caused by cerebral hyperperfusion syndrome after CEA [69]. A more recent study also demonstrated that comprehensive management of hypertension can lower the incidence of ICH and hyperperfusion syndrome in high-risk patients following carotid artery stenting [70].

ICH has been frequently associated with the use of illicit drugs, especially cocaine and amphetamine, which are known to have sympathomimetic effects. Cocaine-induced hypertension is a long-recognized risk factor of ICH. Some patients may also develop a hypertensive encephalopathy with multiple ICH and brain edema [71]. The exact mechanism by which these drugs cause ICH is not yet clear. One possible explanation is that the sudden elevation of blood pressure that occurs immediately after using drugs may cause an existing aneurysm or arteriovenous malformation in the brain to rupture. Interestingly, a higher frequency of an underlying vascular malformation has been noted in cocaine-related hemorrhage compared to amphetamine-related hemorrhage [71, 72].

What is interesting in the issue of blood pressure and ICH is that blood pressure variability measured with the maximal systolic blood pressure and the standard deviation of systolic blood pressure in both hyperacute and acute periods of ICH was well correlated with poor clinical outcomes [73].

Aneurysmal Subarachnoid Hemorrhage

SAH (Fig. 6.6) occurs when a blood vessel near the brain surface leaks, leading to extravasation of blood into the subarachnoid space. SAH is most often caused by rupture of a saccular aneurysm. Saccular aneurysms are most commonly seen at the ICA–posterior communicating artery junction, anterior communicating artery–ACA junction, the apex of basilar artery, and the MCA bifurcation. Histopathologic

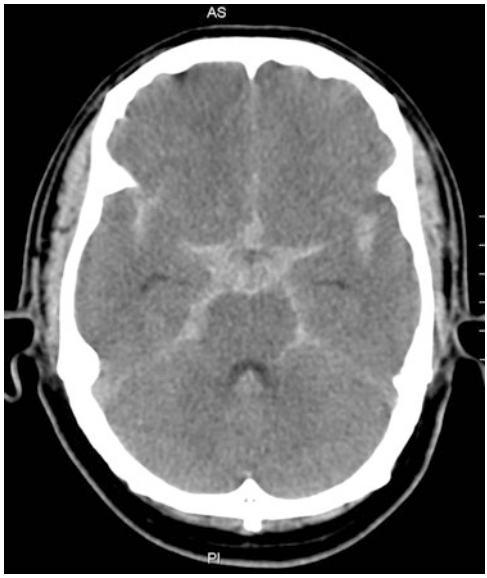

Fig. 6.6 Subarachnoid hemorrhage. Extensive blood clots occupy basal and perimesencephalic cisterns and both sylvian fissures

features of aneurysms include degenerative changes, thinning of the media, inflammatory changes, atherosclerosis, and presence of medial and elastic defects of the aneurysmal wall [74].

The mechanism of the origin, growth, and rupture of saccular intracranial aneurysm is largely unknown. Intracranial arteries are more susceptible to aneurysm formation than extracranial arteries because intracranial vessels are thinner, with less elastin; the external elastic lamina is absent; and vessels in the subarachnoid space lack surrounding supporting tissue. A congenital deficit in the arterial media may be a weak spot through which the inner layers of the arterial wall bulge and is a possible explanation for aneurysmal formation. Focal deficits are often located at arterial bifurcations. Reduced production of type III collagen has also been reported to be associated with familial intracranial aneurysms [75]. In addition, acquired changes in the arterial wall are also likely to be important since hypertension, smoking, and alcohol abuse are known risk factors for SAH. These conditions lead to local thickening of the intimal layer of the arterial wall. This, in turn, may increase strain on the more elastic portions of the vessel wall [76].

In animal models, saccular aneurysms can be produced by combining experimental renal hypertension and ligation of a carotid artery to alter hemodynamic stress in the circle of Willis. However, the administration of beta-aminopropionitrile alone, a potent irreversible inhibitor of lysyl oxidase which initiates cross-linkage formation in elastin and collagen, without the presence of hypertension does not induce aneurysm formation, which indicates that a vascular lesion and hemodynamic stress are both important in the pathogenesis of aneurysm formation [49]. In addition, abnormalities in structural proteins of the extracellular matrix have been identified in the arterial wall at a distance from the aneurysm itself [77].

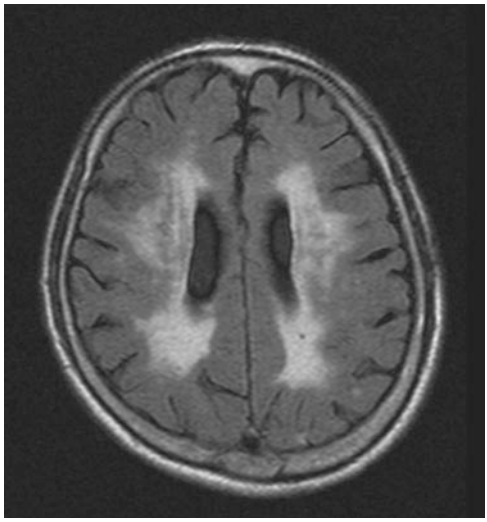

Fig. 6.7 White matter lesions. Extensive white matter changes (leukoaraiosis) are observed in both periventricular and subcortical white matter

Stress on the vessel wall increases as the radius of the aneurysm enlarges. When the wall stress exceeds the wall strength, aneurysms rupture. Evidence indicates that aneurysms larger than 10 mm in diameter are more likely to rupture [78]. Aneurysms may rupture at any time, but are more prone to do so when blood pressure or blood flow increases during strenuous activity.

Mechanisms of Silent Brain Lesions in Relation to Hypertension

White Matter Lesions

White matter lesions (WMLs) (Fig. 6.7) are considered present if visible as hyperintense lesions on proton-density and T2-weighted images, without prominent hypointensity on T1-weighted scans [79]. WMLs are strongly associated with increasing age. However, in most studies, white matter changes are more common in hypertensive than in normotensive individuals, especially in the young. A population-based study showed that the duration of hypertension was associated with both periventricular and subcortical WMLs. Furthermore, subjects with successfully treated hypertension had only moderately increased subcortical and periventricular WMLs compared with normotensive subjects [80]. The importance of WMLs as a predictor of stroke risk [79, 81] and vascular dementia [80] has been demonstrated in previous studies.

The pathology of WML is heterogeneous, including small infarction, gliosis, demyelination, vascular ectasia, and dilated perivascular spaces, all of which are also commonly seen in the experimental hypertension model [82]. The exact mechanism of WMLs is unclear, but hypertension-related arteriolosclerosis appears to be the most important causative factor, and the extent of WMLs is thought to reflect the extent of brain arteriolosclerosis [83].

Silent Infarctions: Old Lacunar Infarcts and Microinfarcts

Silent infarcts may be divided into two comparable categories: old lacunar infarctions and microinfarcts. Old lacunar infarcts are defined as focal hyperintensities on T2-weighted images, 3 mm in size or larger, with corresponding prominent hypointensities on T1-weighted images [79]. Old lacunar infarcts and WMLs are thought to have similar vascular origin. However, the majority of silent infarcts are lacunar infarcts which may be caused by either large or small vessel disease, whereas WMLs reflect mainly small vessel disease. In terms of clinical outcome, studies indicate that both community-based normal elderly people [79, 84] and stroke patients [81, 85] with old lacunar infarcts and WMLs are at a strongly increased risk of stroke, which cannot be explained by other stroke risk factors. Microinfarcts are typically undetected by conventional structural MRI and can be detected only by microscopic histological examinations, although the largest acute microinfarcts can be detected by diffusion-weighted imaging [86, 87]. This category of silent, or at least subclinical, lesions has been associated with macroscopic infarcts and commonly coexists with Alzheimer disease pathology [88, 89].

Cerebral Microbleeds

Microbleeds (MBs) (Fig. 6.8) are defined as punctate, homogeneous, rounded, lesions less than 0.5 cm in size, with signal loss or hypointensity on gradient echo MRI. The pathology of microbleeds is perivascular deposits of hemosiderin in the

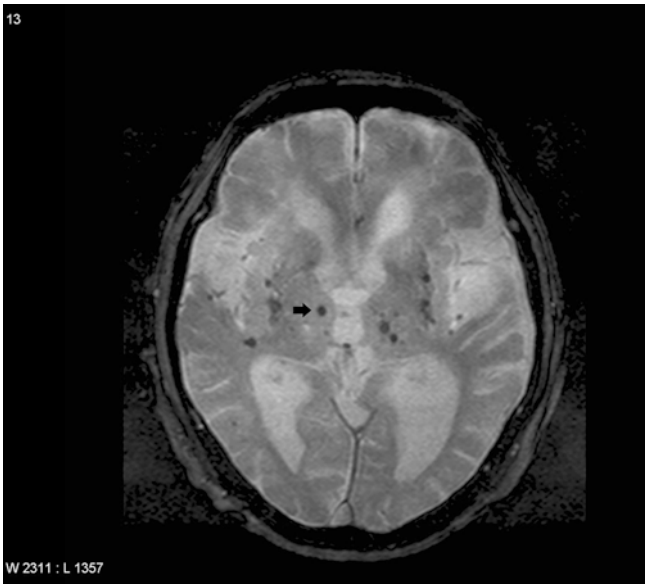

Fig. 6.8 Microbleeds. Several microbleeds are seen in both thalamus and basal ganglia. The *black arrow* indicates one of them. (*Sources*: Figs. 5, 6, 7, and 8 from Dr Bae's collections)

brain, which is regarded as evidence of previous rupture of small vessels [90, 91]. MBs have been found in patients with both ICHs and ischemic stroke. The presence of MBs predicts the recurrence of ICH in patients with primary lobar ICH and is associated with aspirin-associated ICH [92]. Hence, antiplatelet medications should be used with caution in patients with diffuse MBs. Various studies have shown that microbleeds are related with subsequent cerebral bleeding among patients with ischemic stroke including acute hemorrhagic transformation after thrombolysis [93], although there is also some evidence against the importance of MBs as a predictor of hemorrhagic transformation [94]. Lobar microbleeds detected in the elderly are often attributed to amyloid angiopathy and associated with Alzheimer's disease.

The mechanism of microbleedsMicrobleeds (MBs) is largely unknown. MBs have been found to be associated with increased age, hypertension, WMLs, lacunar infarcts, and ICH [95, 96]. One recent study found that there were linear associations between MBs, WMLs, and lacunar infarcts. With increasing number of lacunar infarcts or severity of WMLs, the frequency and the number of MBs increased in parallel [90]. This finding indicates that microbleeds, white matter changes, and lacunar infarcts most probably share the same pathogenesis of advanced microangiopathy.

Conclusions

Hypertension has deleterious effects on the cerebral circulation. Hypertension alters the structure of blood vessels by producing vascular hypertrophy and remodeling and by promoting atherosclerosis in large cerebral arteries and lipohyalinosis in penetrating arterioles. In addition, hypertension also impairs endothelium-dependent relaxation and alters cerebrovascular autoregulation and neurovascular coupling. With these functional and structural alternations, hypertension facilitates vascular occlusions or degenerative change that is prone to rupture and bleeding, thereby causing both ischemic and hemorrhagic stroke. Recently it has been shown that short-term and also long-term blood pressure variability can play a role in the pathogenesis of stroke.

Better understanding of these underlying mechanisms may provide new insights into stroke management and prevention. Since hypertension is one of the modifiable risk factors of cerebrovascular disease, optimal blood pressure control may significantly lower the risk of stroke.

References

1. Gaciong Z, Siński M, Lewandowski J. Blood pressure control and primary prevention of stroke: summary of the recent clinical trial data and meta-analyses. Curr Hypertens Rep. 2013; 15(6):559–74.
2. Kim BJ, Park JM, Kang K, Lee SJ, Ko Y, Kim JG, et al. Case characteristics, hyperacute treatment, and outcome information from the clinical research center for stroke-fifth division registry in South Korea. J Stroke. 2015;17(1):38–53.

3. Kannel WB, Wolf PA, Verter J, McNamara PM. Epidemiologic assessment of the role of blood pressure in stroke. The Framingham study. JAMA. 1970;214(2):301–10.
4. Whisnant JP. Epidemiology of stroke: emphasis on transient cerebral ischemia attacks and hypertension. Stroke. 1974;5(1):68–70.
5. Ohkubo T, Asayama K, Kikuya M, Metoki H, Obara T, Saito S, et al. Prediction of ischaemic and haemorrhagic stroke by self-measured blood pressure at home: the Ohasama study. Blood Press Monit. 2004;9(6):315–20.
6. Ross R. Atherosclerosis—an inflammatory disease. N Engl J Med. 1999;340(2):115–26.
7. Fisher M, Paganini-Hill A, Martin A, Cosgrove M, Toole JF, Barnett HJ, et al. Carotid plaque pathology: thrombosis, ulceration, and stroke pathogenesis. Stroke. 2005;36(2):253–7.
8. Bornstein NM, Krajewski A, Lewis AJ, Norris JW. Clinical significance of carotid plaque hemorrhage. Arch Neurol. 1990;47(9):958–9.
9. Bornstein NM, Norris JW. The unstable carotid plaque. Stroke. 1989;20(8):1104–6.
10. Chen XY, Wong KS, Lam WW, Zhao HL, Ng HK. Middle cerebral artery atherosclerosis: histological comparison between plaques associated with and not associated with infarct in a postmortem study. Cerebrovasc Dis. 2008;25(1–2):74–80.
11. Bodle JD, Feldmann E, Swartz RH, Rumboldt Z, Brown T, Turan TN. High-resolution magnetic resonance imaging: an emerging tool for evaluating intracranial arterial disease. Stroke. 2013;44(1):287–92.
12. Caplan LR. Basic pathology, anatomy, and pathophysiology of stroke. In: Caplan LR, editor. Caplan's stroke: a clinical approach. 3rd ed. Woburn: Butterworth-Heinemann; 2000. p. 17–50.
13. Wong LKS. Global burden of intracranial atherosclerosis. Int J Stroke. 2006;1:158–9.
14. Bang OY, Kim JW, Lee JH, Lee MA, Lee PH, Joo IS, et al. Association of the metabolic syndrome with intracranial atherosclerotic stroke. Neurology. 2005;65(2):296–8.
15. Nam HS, Han SW, Lee JY, Ahn SH, Ha JW, Rim SJ, et al. Association of aortic plaque with intracranial atherosclerosis in patients with stroke. Neurology. 2006;67(7):1184–8.
16. Suh DC, Lee SH, Kim KR, Park ST, Lim SM, Kim SJ, et al. Pattern of atherosclerotic carotid stenosis in Korean patients with stroke: different involvement of intracranial versus extracranial vessels. AJNR Am J Neuroradiol. 2003;24(2):239–44.
17. Nishimaru K, McHenry Jr LC, Toole JF. Cerebral angiographic and clinical differences in carotid system transient ischemic attacks between American Caucasian and Japanese patients. Stroke. 1984;15(1):56–9.
18. Ritz K, Denswil NP, Stam O, van Lieshout JJ. Cause and mechanisms of intracranial atherosclerosis. Circulation. 2014;130(16):1407–14.
19. Norris JW, Zhu CZ, Bornstein NM, Chambers BR. Vascular risks of asymptomatic carotid stenosis. Stroke. 1991;22(12):1485–90.
20. Streifler JY, Eliasziw M, Benavente OR, Harbison JW, Hachinski VC, Barnett HJ, et al. The risk of stroke in patients with first-ever retinal vs hemispheric transient ischemic attacks and high-grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial. Arch Neurol. 1995;52(3):246–9.
21. Kasner SE, Chimowitz MI, Lynn MJ, Howlett-Smith H, Stern BJ, Hertzberg VS, et al. Predictors of ischemic stroke in the territory of a symptomatic intracranial arterial stenosis. Circulation. 2006;113(4):555–63.
22. Wong KS, Li H, Lam WW, Chan YL, Kay R. Progression of middle cerebral artery occlusive disease and its relationship with further vascular events after stroke. Stroke. 2002;33(2):532–6.
23. Kieffer SA, Takeya Y, Resch JA, Amplatz K. Racial differences in cerebrovascular disease. Angiographic evaluation of Japanese and American populations. Am J Roentgenol Radium Ther Nucl Med. 1967;101(1):94–9.
24. Caplan LR, Gorelick PB, Hier DB. Race, sex and occlusive cerebrovascular disease: a review. Stroke. 1986;17(4):648–55.
25. Waddy SP, Cotsonis G, Lynn MJ, Frankel MR, Chaturvedi S, Williams JE, et al. Racial differences in vascular risk factors and outcomes of patients with intracranial atherosclerotic arterial stenosis. Stroke. 2009;40(3):719–25.
26. Hachinski V. Stroke in Korean. Stroke. 2008;39(4):1067.

27. Fisher CM. Observations of the fundus oculi in transient monocular blindness. Neurology. 1959;9(5):333–47.
28. Lhermitte F, Gautier JC, Derouesne C. Nature of occlusions of the middle cerebral artery. Neurology. 1970;20(1):82–8.
29. Caplan LR. Intracranial branch atheromatous disease: a neglected, understudied, and underused concept. Neurology. 1989;39(9):1246–50.
30. Kang SY, Kim JS. Anterior cerebral artery infarction: stroke mechanism and clinical-imaging study in 100 patients. Neurology. 2008;70(24 Pt 2):2386–93.
31. Vemmos KN, Spengos K, Tsivgoulis G, Manios E, Zis V, Vassilopoulos D. Aetiopathogenesis and long-term outcome of isolated pontine infarcts. J Neurol. 2005;252(2):212–7.
32. Wong KS, Gao S, Chan YL, Hansberg T, Lam WW, Droste DW, et al. Mechanisms of acute cerebral infarctions in patients with middle cerebral artery stenosis: a diffusion-weighted imaging and microemboli monitoring study. Ann Neurol. 2002;52(1):74–81.
33. Lee DK, Kim JS, Kwon SU, Yoo SH, Kang DW. Lesion patterns and stroke mechanism in atherosclerotic middle cerebral artery disease: early diffusion-weighted imaging study. Stroke. 2005;36(12):2583–8.
34. Nah H-W, Kang D-W, Kwon SU, Kim JS. Diversity of single small subcortical infarctions according to infarct location and parent artery disease analysis of indicators for small vessel disease and atherosclerosis. Stroke. 2010;41(12):2822–7.
35. Jeong H-G, Kim BJ, Yang MH, Han M-K, Bae H-J. Neuroimaging markers for early neurologic deterioration in single small subcortical infarction. Stroke. 2015;46(3):687–91.
36. Rosenblum WI. Fibrinoid necrosis of small brain arteries and arterioles and miliary aneurysms as causes of hypertensive hemorrhage: a critical reappraisal. Acta Neuropathol. 2008;116(4):361–9.
37. Amano S. Vascular changes in the brain of spontaneously hypertensive rats: hyaline and fibrinoid degeneration. J Pathol. 1977;121(2):119–28.
38. Wiener J, Spiro D, Lattes RG. The cellular pathology of experimental hypertension. II. Arteriolar hyalinosis and fibrinoid change. Am J Pathol. 1965;47:457–85.
39. Lammie GA. Pathology of small vessel stroke. Br Med Bull. 2000;56:296–306.
40. Marti-Vilalta JLAA, Arborix A, Mohr JP. Microangiopathies (Lacunes). In: Mohr JP, Wolf PA, Grotta JC, Moskowitz MA, Mayberg MR, von Kummer R, editors. Stroke: pathophysiology, diagnosis, and management. 5th ed. Philadelphia: Elsevier; 2011. p. 485–515.
41. Hanaway J, Young RR. Localization of the pyramidal tract in the internal capsule of man. J Neurol Sci. 1977;34(1):63–70.
42. Gies J. The pathogenesis of hypertensive vascular disease. Dan Med Bull. 1967;14:259.
43. Fisher CM. Pathological observations in hypertensive cerebral hemorrhage. J Neuropathol Exp Neurol. 1971;30(3):536–50.
44. Fisher CM. Lacunar strokes and infarcts: a review. Neurology. 1982;32(8):871–6.
45. Bang OY, Heo JH, Kim JY, Park JH, Huh K. Middle cerebral artery stenosis is a major clinical determinant in striatocapsular small, deep infarction. Arch Neurol. 2002;59(2):259–63.
46. Okin PM, Wachtell K, Devereux RB, Harris KE, Jern S, Kjeldsen SE, et al. Regression of electrocardiographic left ventricular hypertrophy and decreased incidence of new-onset atrial fibrillation in patients with hypertension. JAMA. 2006;296(10):1242–8.
47. Lee DS, Austin PC, Rouleau JL, Liu PP, Naimark D, Tu JV. Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. JAMA. 2003;290(19):2581–7.
48. Ingelsson E, Bjorklund-Bodegard K, Lind L, Arnlov J, Sundstrom J. Diurnal blood pressure pattern and risk of congestive heart failure. JAMA. 2006;295(24):2859–66.
49. Johansson BB. Hypertension mechanisms causing stroke. Clin Exp Pharmacol Physiol. 1999;26(7):563–5.
50. Wong KS, Caplan LR, Kim JS. Stroke mechanisms. In: Kim JS, Caplan LR, Wong KS, editors. Intracranial atherosclerosis. 1st ed. West Sussex: Wiley-Blackwell; 2008. p. 57–68.
51. Caplan LR, Hennerici M. Impaired clearance of emboli (washout) is an important link between hypoperfusion, embolism, and ischemic stroke. Arch Neurol. 1998;55(11):1475–82.
52. Caplan LR, Wong KS, Gao S, Hennerici MG. Is hypoperfusion an important cause of strokes? If so, how? Cerebrovasc Dis. 2006;21(3):145–53.

53. Nagai M, Kario K. Visit-to-visit blood pressure variability, silent cerebral injury, and risk of stroke. Am J Hypertens. 2013;26(12):1369–76.
54. Parati G, Liu X, Ochoa JE, Bilo G. Prognostic relevance of blood pressure variability: role of long-term and very long-term blood pressure changes. Hypertension. 2013;62(4):682–4.
55. Stolarz-Skrzypek K, Thijs L, Li Y, Hansen TW, Boggia J, Kuznetsova T, et al. Short-term blood pressure variability in relation to outcome in the International Database of Ambulatory blood pressure in relation to Cardiovascular Outcome (IDACO). Acta Cardiol. 2011;66(6):701–6.
56. Kannel WB, Dawber TR, Sorlie P, Wolf PA. Components of blood pressure and risk of atherothrombotic brain infarction: the Framingham study. Stroke. 1976;7(4):327–31.
57. Mancia G, Bombelli M, Facchetti R, Madotto F, Corrao G, Trevano FQ, et al. Long-term prognostic value of blood pressure variability in the general population: results of the Pressioni Arteriose Monitorate e Loro Associazioni Study. Hypertension. 2007;49(6):1265–70.
58. Muntner P, Shimbo D, Diaz KM, Newman J, Sloan RP, Schwartz JE. Low correlation between visit-to-visit variability and 24-h variability of blood pressure. Hypertens Res. 2013;36(11):940–6.
59. Rothwell PM, Howard SC, Dolan E, et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. Lancet. 2010;375(9718):895–905.
60. Ekbom T, Dahlöf B, Hansson L, Lindholm LH, Odén A, Scherstén B, et al. The stroke preventive effect in elderly hypertensives cannot fully be explained by the reduction in office blood pressure—insights from the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension). Blood Press. 1992;1(3):168–72.
61. Hastie CE, Jeemon P, Coleman H, McCallum L, Patel R, Dawson J, et al. Long-term and ultra long-term blood pressure variability during follow-up and mortality in 14,522 patients with hypertension. Hypertension. 2013;62(4):698–705.
62. Diaz KM, Tanner RM, Falzon L, Levitan EB. Visit-to-visit variability of blood pressure and cardiovascular disease and all-cause mortality a systematic review and meta-analysis. Hypertension. 2014;64(5):965–82.
63. Ariesen MJ, Claus SP, Rinkel GJ, Algra A. Risk factors for intracerebral hemorrhage in the general population: a systematic review. Stroke. 2003;34(8):2060–5.
64. Broderick J, Brott T, Tomsick T, Leach A. Lobar hemorrhage in the elderly. The undiminishing importance of hypertension. Stroke. 1993;24(1):49–51.
65. Challa VR, Moody DM, Bell MA. The Charcot-Bouchard aneurysm controversy: impact of a new histologic technique. J Neuropathol Exp Neurol. 1992;51(3):264–71.
66. Takebayashi S, Kaneko M. Electron microscopic studies of ruptured arteries in hypertensive intracerebral hemorrhage. Stroke. 1983;14(1):28–36.
67. Bahemuka M. Primary intracerebral hemorrhage and heart weight: a clinicopathologic case-control review of 218 patients. Stroke. 1987;18(2):531–6.
68. Brott T, Thalinger K, Hertzberg V. Hypertension as a risk factor for spontaneous intracerebral hemorrhage. Stroke. 1986;17(6):1078–83.
69. Ogasawara K, Sakai N, Kuroiwa T, Hosoda K, Iihara K, Toyoda K, et al. Intracranial hemorrhage associated with cerebral hyperperfusion syndrome following carotid endarterectomy and carotid artery stenting: retrospective review of 4494 patients. J Neurosurg. 2007;107(6):1130–6.
70. Abou-Chebl A, Reginelli J, Bajzer CT, Yadav JS. Intensive treatment of hypertension decreases the risk of hyperperfusion and intracerebral hemorrhage following carotid artery stenting. Catheter Cardiovasc Interv. 2007;69(5):690–6.
71. Nolte KB, Brass LM, Fletterick CF. Intracranial hemorrhage associated with cocaine abuse: a prospective autopsy study. Neurology. 1996;46(5):1291–6.
72. McEvoy AW, Kitchen ND, Thomas DG. Intracerebral haemorrhage and drug abuse in young adults. Br J Neurosurg. 2000;14(5):449–54.
73. Manning L, Hirakawa Y, Arima H, Wang X, Chalmers J, Wang J, et al. Blood pressure variability and outcome after acute intracerebral haemorrhage: a post-hoc analysis of INTERACT2, a randomised controlled trial. Lancet Neurol. 2014;13(4):364–73.
74. Sekhar LN, Heros RC. Origin, growth, and rupture of saccular aneurysms: a review. Neurosurgery. 1981;8(2):248–60.
75. de Paepe A, van Landegem W, de Keyser F, de Reuck J. Association of multiple intracranial aneurysms and collagen type III deficiency. Clin Neurol Neurosurg. 1988;90(1):53–6.

76. van Gijn J, Rinkel GJ. Subarachnoid haemorrhage: diagnosis, causes and management. Brain. 2001;124(Pt 2):249–78.
77. Chyatte D, Reilly J, Tilson MD. Morphometric analysis of reticular and elastin fibers in the cerebral arteries of patients with intracranial aneurysms. Neurosurgery. 1990;26(6):939–43.
78. International Study of Unruptured Intracranial Aneurysms Investigators. Unruptured intracranial aneurysms—risk of rupture and risks of surgical intervention. International Study of Unruptured Intracranial Aneurysms Investigators. N Engl J Med. 1998;339(24):1725–33.
79. Vermeer SE, Hollander M, van Dijk EJ, Hofman A, Koudstaal PJ, Breteler MM, et al. Silent brain infarcts and white matter lesions increase stroke risk in the general population: the Rotterdam Scan Study. Stroke. 2003;34(5):1126–9.
80. de Leeuw FE, de Groot JC, Oudkerk M, Witteman JC, Hofman A, van Gijn J, et al. Hypertension and cerebral white matter lesions in a prospective cohort study. Brain. 2002;125(Pt 4):765–72.
81. Fu JH, Lu CZ, Hong Z, Dong Q, Luo Y, Wong KS. Extent of white matter lesions is related to acute subcortical infarcts and predicts further stroke risk in patients with first ever ischaemic stroke. J Neurol Neurosurg Psychiatr. 2005;76(6):793–6.
82. Fazekas F, Kleinert R, Offenbacher H, Schmidt R, Kleinert G, Payer F, et al. Pathologic correlates of incidental MRI white matter signal hyperintensities. Neurology. 1993;43(9):1683–9.
83. van Swieten JC, van den Hout JH, van Ketel BA, Hijdra A, Wokke JH, van Gijn J. Periventricular lesions in the white matter on magnetic resonance imaging in the elderly. A morphometric correlation with arteriolosclerosis and dilated perivascular spaces. Brain. 1991;114(Pt 2):761–74.
84. Vermeer SE, Koudstaal PJ, Oudkerk M, Hofman A, Breteler MM. Prevalence and risk factors of silent brain infarcts in the population-based Rotterdam Scan Study. Stroke. 2002;33(1):21–5.
85. Yamauchi H, Fukuda H, Oyanagi C. Significance of white matter high intensity lesions as a predictor of stroke from arteriolosclerosis. J Neurol Neurosurg Psychiatr. 2002;72(5):576–82.
86. Arvanitakis Z, Leurgans SE, Barnes LL, Bennett DA, Schneider JA. Microinfarct pathology, dementia, and cognitive systems. Stroke. 2011;42(3):722–7.
87. Smith EE, Schneider JA, Wardlaw JM, Greenberg SM. Cerebral microinfarcts: the invisible lesions. Lancet Neurol. 2012;11(3):272–82.
88. Longstreth Jr WT, Sonnen JA, Koepsell TD, Kukull WA, Larson EB, Montine TJ. Associations between microinfarcts and other macroscopic vascular findings on neuropathologic examination in 2 databases. Alzheimer Dis Assoc Disord. 2009;23(3):291–4.
89. Neuropathology Group Medical Research Council Cognitive Function and Aging Study. Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). Lancet. 2001;357(9251):169–75.
90. Fan YH, Mok VC, Lam WW, Hui AC, Wong KS. Cerebral microbleeds and white matter changes in patients hospitalized with lacunar infarcts. J Neurol. 2004;251(5):537–41.
91. Wong KS, Chan YL, Liu JY, Gao S, Lam WW. Asymptomatic microbleeds as a risk factor for aspirin-associated intracerebral hemorrhages. Neurology. 2003;60(3):511–3.
92. Greenberg SM, Eng JA, Ning M, Smith EE, Rosand J. Hemorrhage burden predicts recurrent intracerebral hemorrhage after lobar hemorrhage. Stroke. 2004;35(6):1415–20.
93. Kidwell CS, Saver JL, Villablanca JP, Duckwiler G, Fredieu A, Gough K, et al. Magnetic resonance imaging detection of microbleeds before thrombolysis: an emerging application. Stroke. 2002;33(1):95–8.
94. Kakuda W, Thijs VN, Lansberg MG, Bammer R, Wechsler L, Kemp S, et al. Clinical importance of microbleeds in patients receiving IV thrombolysis. Neurology. 2005;65(8):1175–8.
95. Roob G, Lechner A, Schmidt R, Flooh E, Hartung HP, Fazekas F. Frequency and location of microbleeds in patients with primary intracerebral hemorrhage. Stroke. 2000;31(11):2665–9.
96. Kinoshita T, Okudera T, Tamura H, Ogawa T, Hatazawa J. Assessment of lacunar hemorrhage associated with hypertensive stroke by echo-planar gradient-echo T2*-weighted MRI. Stroke. 2000;31(7):1646–50.