Hypertension

Cerebral Circulation in Hypertension

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The functional integrity of the cerebrovascular system is important when considering the morbidity from hypertension. Several studies have clearly shown the relation that chronic hypertension has on the incidence of thrombotic and nonthrombotic stroke (Kannel, 1974; Shekelle et al, 1974). In addition, alterations in cerebral function and circulation often present as a complication of the treatment of hypertension, especially in the elderly (Jackson, et al, 1976). This presentation will review some basic concepts of the regulation of cerebral blood flow and their significance in the consideration of antihypertensive therapy and their importance in the pathogenesis of hypertensive encephalopathy.

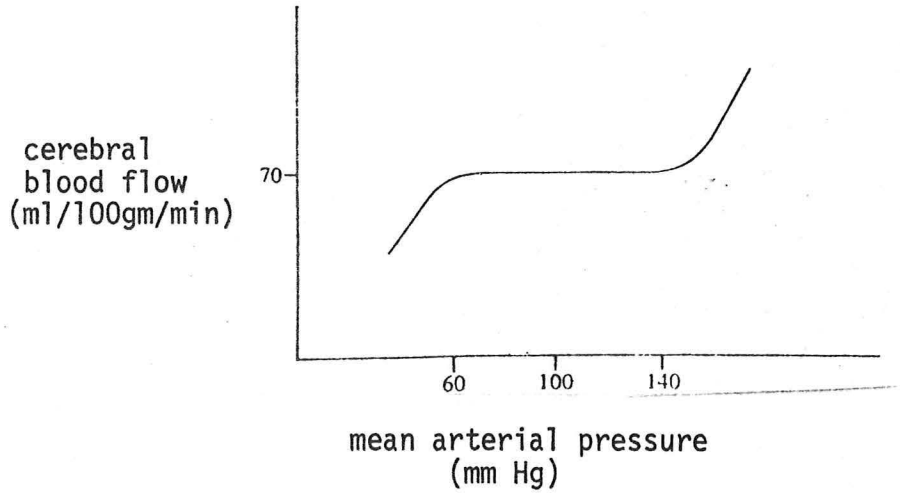
NORMAL AUTOREGULATION OF CEREBRAL BLOOD FLOW

Cerebral blood flow is normally autoregulated such that blood flow is kept fairly constant despite changes in arterial blood pressure. Although autoregulation of blood flow is a property of many vascular systems in the body it is particularly well developed and has been extensively studied in the brain.

The present concept of autoregulation probably began with the observation of autoregulatory vascular responses by Bayliss in 1902. Later, Fogg (1937) noted changes in pial vessel caliber during changes in perfusion pressure. He thought that these changes in caliber probably were involved in the regulation of cerebral blood flow and questioned the accepted view at that time that the cerebral circulation was passive to changes in pressure. Since that time a large number of studies have documented the existence of a complicated mechanism of cerebral blood flow autoregulation.

The presently accepted cerebral blood flow autoregulatory curve is illustrated in Figure 1.

Figure 1.

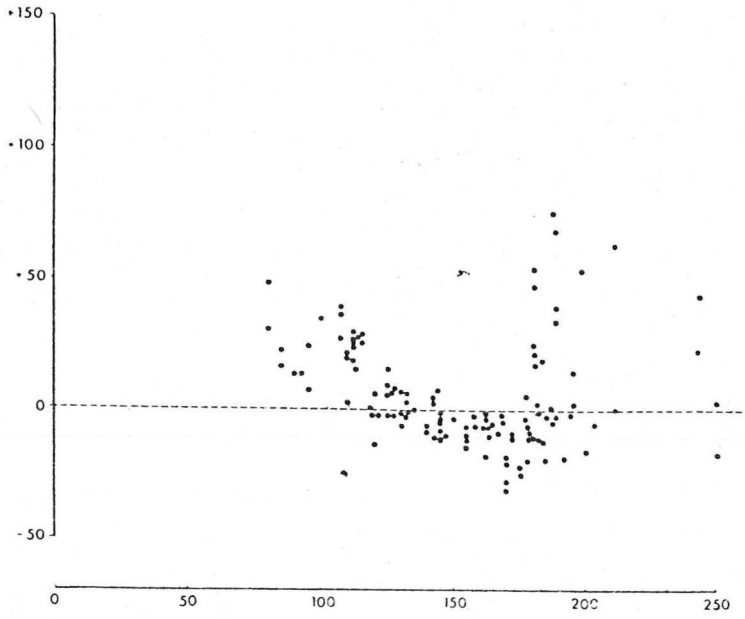


Effect of changes in mean arterial pressure on cerebral blood flow in normal persons.

The delineation of this autoregulatory curve has been accomplished in large part by Lassen and Strandgaard (1974) by utilizing the arterial-venous oxygen difference method for estimating cerebral blood flow. Hypertension was induced by the intravenous infusion of some vasopressor agent that has little direct effect on cerebrovascular resistance at the doses used. Angiotensin II amide is frequently used for this purpose because it has been found to have no effect on regional cerebral blood flow when infused into the internal carotid artery (Olesen, 1972; Agnoli et al, 1965). It should be noted however that angiotensin II does cause activation of the sympathetic nervous system when infused into the vertebral artery. (Ferrario et al, 1972). Trimethaphan, a ganglionic blocking agent, has been used to define the lower region of the autoregulatory curve by inducing controlled hypotension. This is generally accomplished by combining an intravenous infusion of 0.25 to 2 mg per minute and a head-up tilt. Trimethaphan has been used because Olesen (1973) could find no effect on cerebral blood flow when this drug was infused into the internal carotid artery at doses of 0.125 to 2.5 mg per minute. Consequently any changes in cerebral blood flow that occur when this drug is infused have been assumed to be due to a direct effect of the blood pressure change rather than a pharmacologic action of the drug.

Utilizing methods of controlled hypertension and hypotension in normal humans and animals, the concept of autoregulation has been fairly well demonstrated. As blood pressure rises, cerebral blood flow is maintained at a constant level due to vasoconstriction of resistance vessels. If blood pressure continues to rise an upper limit of autoregulation will be reached at a point where vasoconstriction is at a maximum. Further increases in blood pressure result in an increase in the caliber of these resistance vessels with a subsequent increase in cerebral blood flow (Strandgaard et al, 1975). This response to induced hypertension by the small resistance vessels has been demonstrated by MacKenzie et al (1976) utilizing a television image splitting technique in cats. In this study increasing mean arterial pressure led to a decrease in the caliber of the small arterioles until mean arterial pressure reached approximately 170 mm Hg. At this point, arterial dilatation occurred and cerebral blood flow increased. Figure 2 illustrates the relation of arteriolar caliber to mean arterial pressure.

Figure 2.



The effect of increasing mean arterial blood pressure on the caliber of pial arterioles (Mackenzie, et al, 1976).

The increase in blood flow that occurs at very high arterial pressures has important clinical implications which will be discussed in the the section dealing with hypertensive encephalopathy.

When blood pressure falls, cerebral blood flow is maintained by dilatation of the cerebral vessels. However, a lower limit of autoregulation can be reached at a point where resistance vessels are maximally vasodilated. Any further fall in blood pressure from this point will result in a fall in cerebral blood flow. The lower limit of cerebral blood flow autoregulation in normal persons is at a mean arterial pressure of approximately 50-70 mm Hg if measured using trimethaphan induced hypotension (Strandgaard et al, 1973). It should be noted, however, that hypotension induced by other mechanisms that leave the sympathetic nervous system intact, such as hemorrhage, is tolerated less well. In these situations cerebral blood flow declines at higher mean arterial pressures because of reflex sympathetic vasoconstriction of the cerebral arteries.

MECHANISMS OF AUTOREGULATION

Certain aspects regarding the reactivity of the cerebral vessels to changes in blood pressure can be explained by mechanisms involving myogenic, metabolic and neurogenic factors. According to the myogenic hypothesis, the smooth muscle of the arterial wall of the cerebral vessel changes its tone reflexly in response to changes in arterial blood pressure. The observation that the initial component of the autoregulatory response occurs within seconds of a change in blood pressure and the fact that pulsating pressure causes greater vasoconstriction than static pressure support this hypothesis. The metabolic hypothesis states that cerebral blood flow is regulated to the metabolic need of the brain tissue. It is well established that global cerebral blood flow is directly proportional to the metabolic activity of the cerebral cortex. Consequently, cerebral blood flow is low in patients with coma and very high in areas of great metabolic need from neuronal activity. Studies have shown a marked increase in cerebral blood flow and fall in cerebral vascular resistance in areas of epileptic activity (Maekawa et al, 1984). Several metabolic factors influence cerebral blood flow including carbon dioxide, oxygen and pH. In addition, significant hypoxia and hypercapnia will completely abolish the brains ability to autoregulate cerebral blood flow. However, it has not been proven that any of these metabolic factors influence the normal autoregulation of cerebral blood flow to changes in blood pressure.

The third hypothesis to explain the mechanism of autoregulation of cerebral blood flow involves the sympathetic nervous system. Several observations have lead investigators to believe that the sympathetic nervous system has a significant influence on the tone of the cerebral resistance vessels. Cerebral blood flow is depressed in hemorrhagic shock to a greater degree than a similar level of shock induced by ganglionic blockade or hemorrhagic shock after sympathectomy (Fitch et al, 1975). This has been interpreted to mean that the sympathetic nervous system, when activated by hemorrhagic shock, increases the tone of the resistance vessels and thereby decreases cerebral blood flow. In addition, recent studies in man have demonstrated the existence of alpha receptors, especially α_1, in cerebral vessels (Skärby et al, 1983; Toda, 1983) The presence of these receptors implies at least some modulation of cerebral blood flow by the sympathetic nervous system or circulating catecholamines (Harper et al, 1972). However, other studies have failed to show much influence of sympathetic blockade on the upper limit of autoregulation of cerebral blood flow (Waltz et al, 1971).

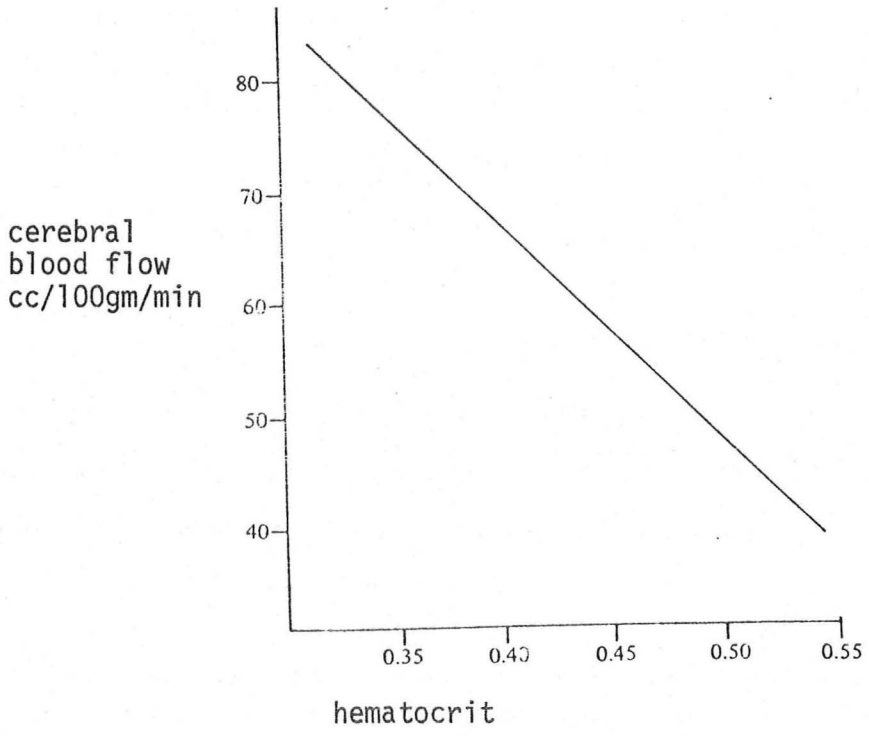
OTHER FACTORS INFLUENCING CEREBRAL BLOOD FLOW

Several factors other than blood pressure have been shown to influence cerebral blood flow. Intracranial pressure can markedly influence regional and global cerebral blood flow. It has generally been accepted that cerebral blood flow is minimally affected by increases in intracranial pressure until pressures of 450 mm of water or greater are reached. As intracranial pressure rises, arterial blood pressure usually increases thereby maintaining cerebral blood flow.

However, when intracranial pressure equals arterial blood pressure, cerebral blood flow ceases. The rate of increase of intracranial pressure is also important in that acute changes affect cerebral blood flow more than chronic changes. Studies by Nagao et al (1984) indicate that increases in intracranial pressure influence the upper brain stem before the lower brain stem and that the Cushing response is very important in maintaining regional cerebral blood flow to the medulla oblongata.

Hematocrit, being an important determinant of blood viscosity, can affect cerebral blood flow significantly. The relationship of hematocrit to cerebral blood flow is illustrated in figure 3.

Figure 3.

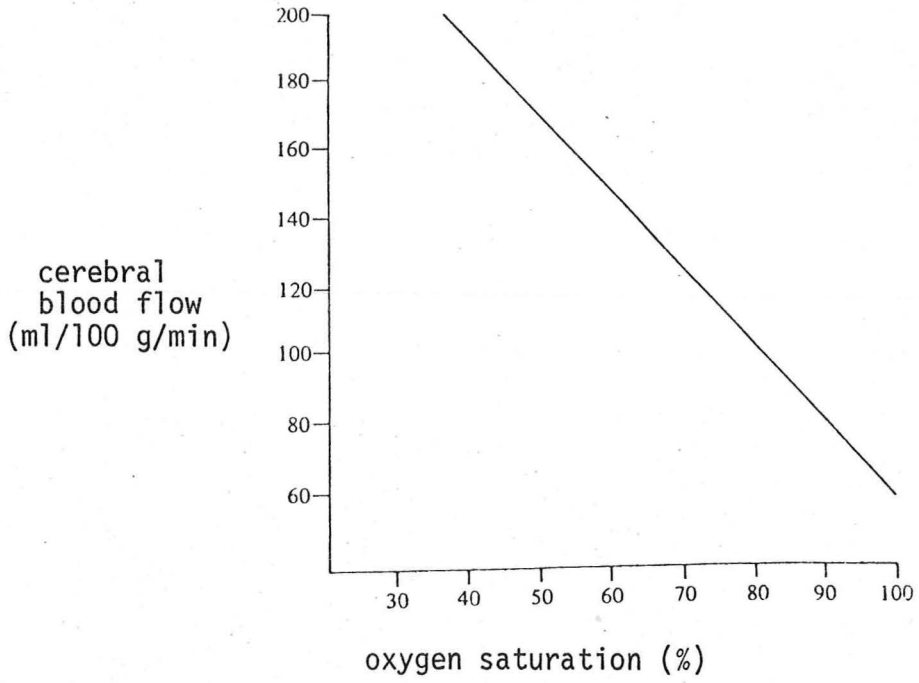


Relationship between hematocrit and cerebral blood flow.

This relationship has important clinical significance. For example, patients with polycythemia vera in general exhibit a decrease in cerebral blood flow and phlebotomy in these patients results in an increase in cerebral blood flow even though cardiac performance may not change significantly (Kahtinen and Kuikka, 1983).

Changes in arterial oxygen saturation have important influences on cerebral blood flow in that there is a linear relationship between cerebral blood flow and arterial oxygen content (figure 4).

Figure 4.

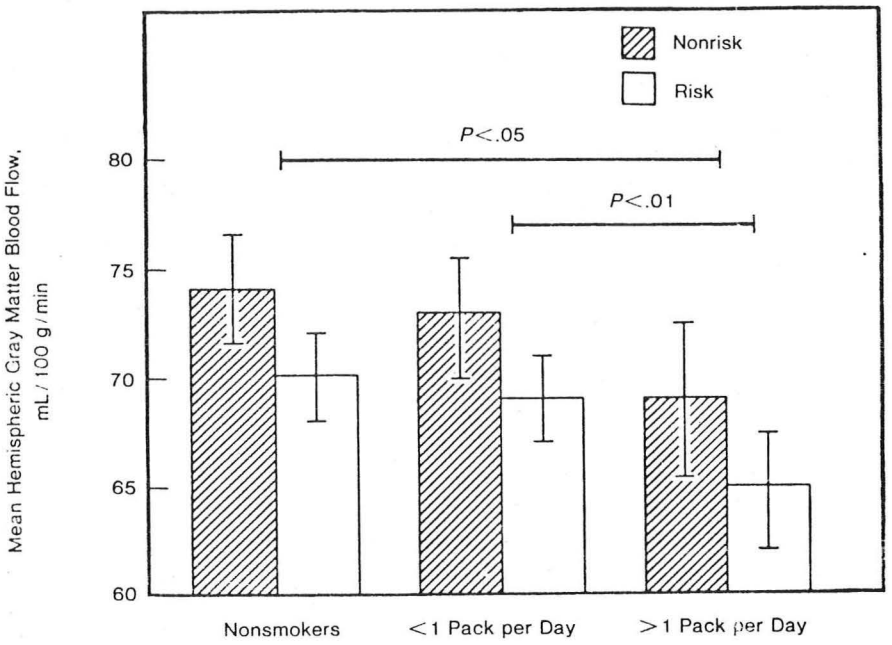


Relationship of cerebral blood flow to oxygen content of blood.

Obviously this is of little importance when arterial oxygenation is near normal and is clinically significant only when the PaO_2 is below about 60 mm Hg because of the configuration of the oxygen hemoglobin dissociation curve. Below this level cerebral blood flow increases in an effort to maintain an adequate oxygen supply to the brain. Increasing PaO_2 above normal has a small effect on cerebral blood flow in that breathing 100% oxygen will decrease cerebral blood flow by about 10%.

Similarly chronic cigarette abuse has been noted to affect cerebral blood flow. Rogers et al (1984) reported that persons who smoke more than one pack of cigarettes per day have significantly lower gray matter blood flows than nonsmokers. This was especially true in those patients who had other risk factors for stroke, such as hypertension, heart disease, diabetes mellitus or hyperlipidemia. The results of this study are shown in figure 5.

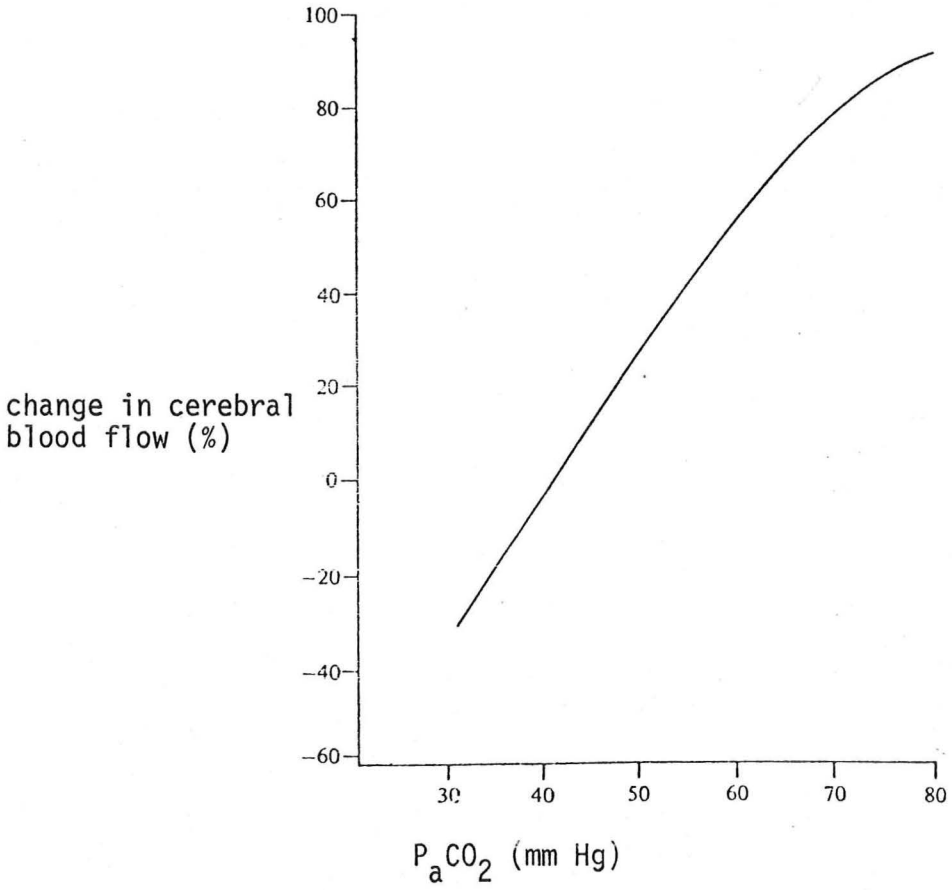
Figure 5.



Mean hemispheric gray matter blood flow values for nonsmokers, those who smoke less than one pack per day, and those who smoke more than one pack per day in subjects with and without other accepted risk factors for stroke (hypertension, heart disease, diabetes and hyperlipidemia). All means are adjusted for age, sex, and level of chronic alcohol consumption (Rogers et al, 1984).

Arterial carbon dioxide also has an important influence on cerebral blood flow as illustrated in figure 6. The changes that are shown occur with acute manipulations of $PaCO_2$. Chronic changes in $PaCO_2$ have little effect on cerebral blood flow indicating that arterial and cerebrospinal fluid pH probably mediate the changes that occur acutely with changing ventilation.

Figure 6.

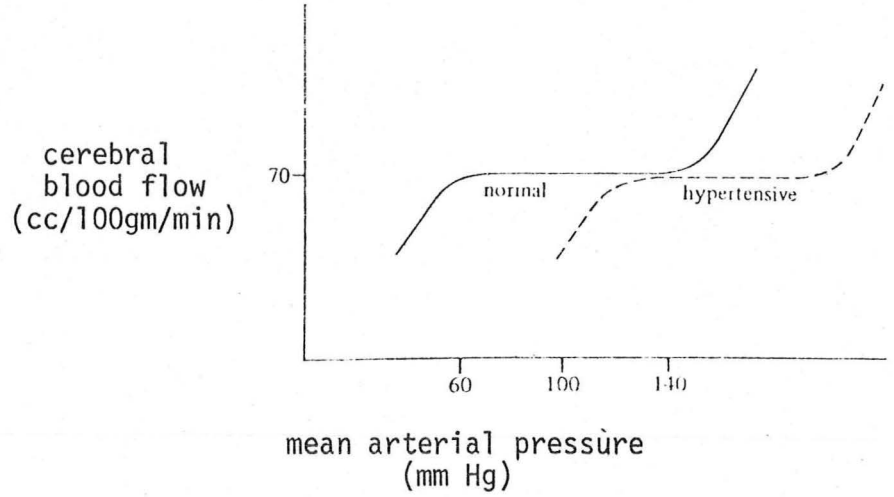


Relationship of cerebral blood flow to P_aCO_2.

EFFECTS OF HYPERTENSION ON CEREBRAL BLOOD FLOW AUTOREGULATION

Although baseline cerebral blood flow is normal or near normal (approximately 50cc/100gm/min) in chronically hypertensive patients, the autoregulatory curve is shifted to the right (Figure 7).

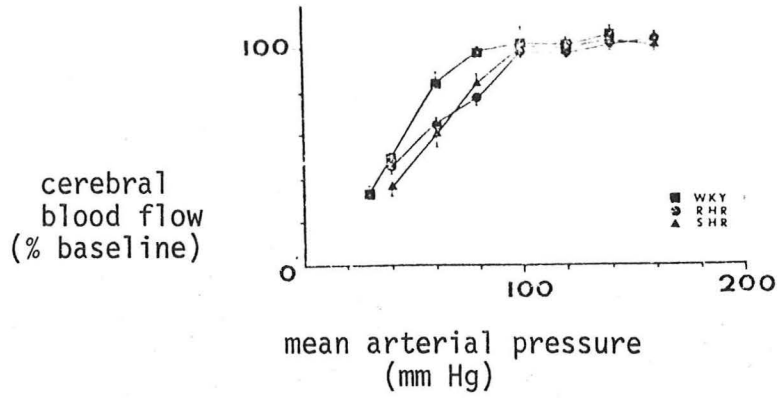
Figure 7.



The effect of chronic hypertension on cerebral blood flow autoregulation.

The effects of chronic hypertension on the lower limit of autoregulation have been extensively studied. In normotensive persons, cerebral blood flow begins to fall at mean arterial pressures of approximately 50-80 mm Hg (Lassen, 1959; Strandgaard, 1978). However, in persons with severe hypertension, the point at which autoregulation begins to fail is shifted upward to a mean arterial pressure of around 110 mm Hg (range 85-150 mm Hg) (Strangaard, 1978). The shift of the lower limit of autoregulation to the right in chronically hypertensive animals has been studied in some detail by Barry et al. (1982) using spontaneously and renal hypertensive rats. Their data (figure 8) illustrates that hypertension of approximately two months duration resets the lower limit of cerebral blood flow autoregulation to a level 20-30 mm Hg higher than the level found in normal animals. In this study blood pressure was raised with angiotensin II and lowered with controlled hemorrhagic hypotension.

Figure 8.



Lower part of the cerebral blood flow autoregulation curve in normotensive rats (WKY), renal hypertensive rats (RHR) and spontaneously hypertensive rats (SHR) (Barry et al, 1982).

In this study the sensitivity of the cerebral circulation to the effects of similar levels of hypotension in the three groups of animals was judged by pathological evidence of ischemic brain damage. Histologic evidence of such damage was found in one of six normotensive animals, four of eight animals with renal vascular hypertension and two of four spontaneously hypertensive animals. The lesions found were small ischemic foci distributed in the cortex, caudatum, hippocampus, and thalamus of the right cerebral cortex.

The duration of hypertension is also important in the adaptive changes that occur with chronic hypertension. This influence has been demonstrated by Fujishima, et al. (1984) by comparing the cerebral blood flow autoregulatory responses of aged (26.3 months) and young (3.4 months) spontaneously hypertensive rats. Baseline cortical blood flow was similar in both groups but the aged animals required less of a drop in mean arterial blood pressure to significantly reduce cortical and thalamic blood flow (Table I).

Table I.

	Young SHR	Aged SHR
Cortical CBF		
10% Reduction		
ΔMAP (mm Hg)	48±6	27±4**
ΔMAP/MAP (%)	28±4	14±2***
20% Reduction		
ΔMAP (mm Hg)	70±4	45±5***
ΔMAP/MAP (%)	42±3	26±3***
Thalamic CBF		
10% Reduction		
ΔMAP (mm Hg)	46±9	24±4*
ΔMAP/MAP (%)	28±6	14±2*
20% Reduction		
ΔMAP (mm Hg)	69±8	40±5***
ΔMAP/MAP (%)	41±5	23±3***

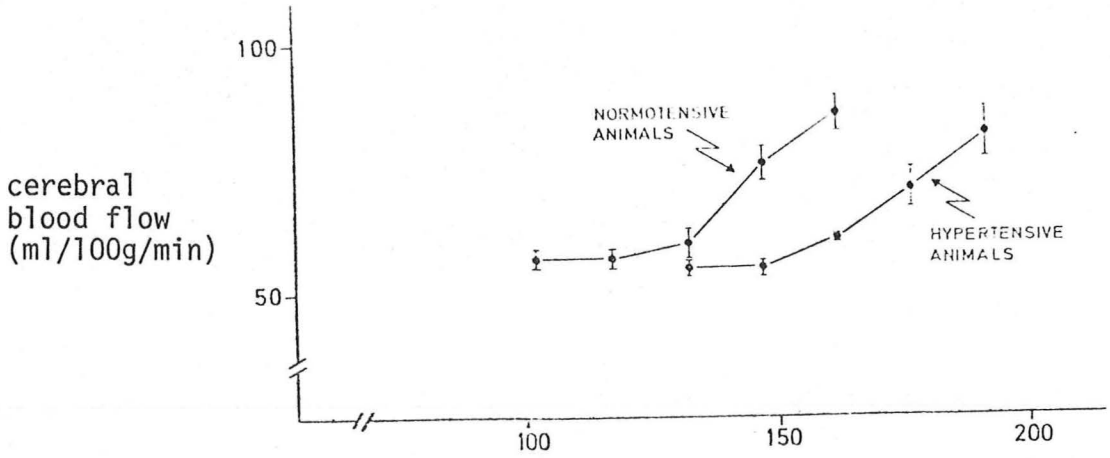
*$p<0.05$ **$p<0.01$ ***$p<0.005$

Absolute (ΔMAP) and percent changes (ΔMAP/MAP) of mean arterial pressure (MAP) from resting value at 10 and 20% reduction of CBF during hemorrhagic hypotension in young and aged SHR. (Fujishima et al, 1984).

This study suggests that the adaptive changes that occur with hypertension are dependent on the duration of the disease. These findings have important clinical relevance when treating elderly persons with hypertension.

The upper limit of cerebral blood flow autoregulation is also shifted to the right as demonstrated by figure 9 from Strandgaard et al, (1975).

Figure 9.



Autoregulation of cerebral blood flow in hypertensive and normotensive baboons.

In this study, baboons made hypertensive by unilateral renal artery constriction were studied before and after 2 to 3 months of hypertension. The upper limit of autoregulation was shifted to higher mean arterial pressures after the animals were made hypertensive, and the shift was of a similar magnitude as the shift to the right of the lower limit of autoregulation.

HYPERTENSIVE ENCEPHALOPATHY

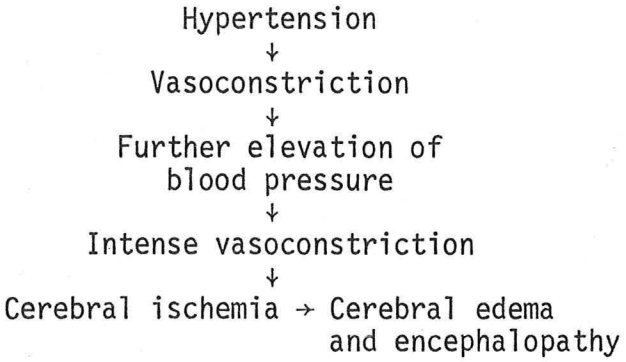
Hypertensive encephalopathy is a serious clinical disorder and the most commonly encountered hypertensive crisis. The pathogenesis and clinical characteristics of this disorder are closely tied to abnormalities in cerebral blood flow autoregulation. The clinical characteristics of this disorder are varied, but symptoms generally occur in patients whose blood pressure is acutely elevated from their baseline levels. A generalized headache of varying severity is usually the first symptom. Nausea, vomiting and visual changes are very common. Many patients complain of focal neurologic symptoms and seizures may occur. Alterations in mental status ranging from drowsiness to coma characterize this disorder. Fundiscopic abnormalities found with this disorder include papilledema, flame shaped retinal hemorrhages and exudates. The presence of significant hypertension, headache, alterations of mental status, papilledema, seizures or neurologic symptoms should suggest the diagnosis of hypertensive encephalopathy. The clinician, however, must remember that elevations of blood pressure may accompany other neurologic conditions and the significance of

hypertension in a patient with new neurologic symptoms should be carefully assessed.

The pathogenesis of hypertensive encephalopathy has been debated for several years. Focal or generalized cerebral edema characterized by an increase in brain weight, depression of the ventricles, and flattening of the gyri is the most significant pathological finding in hypertensive encephalopathy. Acute fibrinoid necrosis in penetrating cerebral arteries, petechial hemorrhages, small infarcts and perivascular exudates are frequently found on pathologic examination in addition to cerebral edema. Patients with hypertensive encephalopathy many times will also demonstrate pathologic changes due to chronic hypertension such as atherosclerosis, medial hypertrophy of the vessel wall and hyalinization.

Byrom (1954) felt that the cerebral edema was due to ischemic vascular damage from the intense reflex vasoconstriction that occurs with significant elevation of blood pressure. He felt that this intense vasoconstriction led to a decrease in cerebral blood flow resulting in ischemia and cerebral edema.

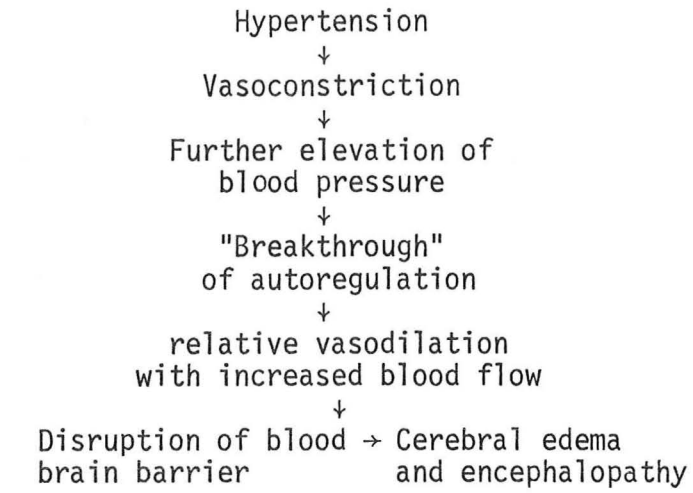
Figure 10.



Early concept of the pathogenesis of hypertensive encephalopathy (Byrom, 1954).

However, studies by Strangaard, et al, (1974) suggest that the development of cerebral edema in hypertensive encephalopathy is due to a "breakthrough" of autoregulation with a marked increase in cerebral blood flow rather than ischemia. As noted previously, severe elevations in blood pressure can lead to an increase in cerebral blood flow after the upper limit of autoregulation is exceeded. This marked increase in flow is thought to result in vascular damage with disruption of the blood brain barrier and subsequent cerebral edema (Figure 11).

Figure 11.

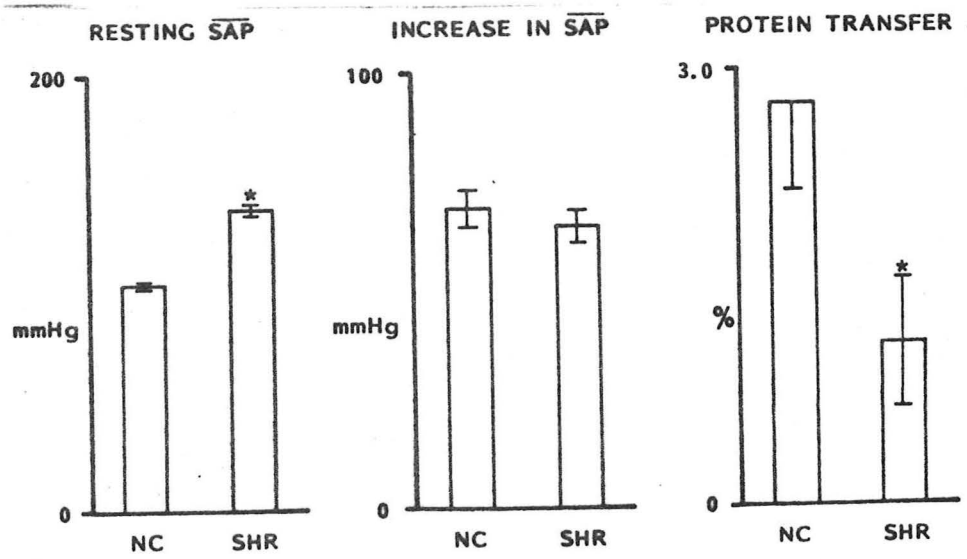


Pathogenesis of hypertensive encephalopathy (Johansson, 1974).

Disruption of the blood brain barrier with a subsequent increase in its permeability to protein bound dyes has been shown to occur very rapidly after the induction of severe acute hypertension in animals (Nag, 1977). However, the permeability of the cerebral vessels to water can increase independently of permeability changes to protein, and such water flux maybe important in the development of the cerebral edema of hypertensive encephalopathy. Studies of cerebral blood flow and hypertensive encephalopathy have generally found flows to be normal (McCall, 1949; Moyer, 1953) or decreased (Finnerty, 1974). While these studies appear to contradict those that suggest that the "breakthrough" of autoregulation is responsible (Johsansson, 1974), it must be remembered that in most cases cerebral blood flow has been measured after significant cerebral edema has developed. The increase in intracranial pressure that ensues when cerebral edema is present will cause a decrease in cerebral blood flow. Sadoshima (1982) found that stroke prone spontaneously hypertensive rats with encephalopathy demonstrated focal disruption of the blood brain barrier without evidence of ischemic infarction or hemorrhage. This led Tomaki (1984) to examine cerebral blood flow in hypertensive encephalopathy in animals and its relation to cerebral edema. This study had several important conclusions. First, in animals with hypertensive encephalopathy without stroke, regional cerebral blood flow was normal or increased in areas with disruption of the blood brain barrier and minimal edema. This is contrary to the concept that vasospasm and ischemia causes the disruption of the blood brain barrier and suggests that the disruption of the blood brain barrier precedes ischemia. Second, in regions with severe brain edema regional cerebral blood flow was reduced. This finding offers a possible explanation as to why many studies of cerebral blood flow in hypertensive encephalopathy find a decrease in global cerebral blood flow.

Factors other than the absolute value of blood pressure are important in the pathogenesis of or protection from hypertensive encephalopathy. First, the presence of chronic arterial hypertension provides some protection from the development of this disorder. As noted previously chronic hypertension shifts the cerebral blood flow autoregulatory curve to the right. The implications of this on the upper limit of cerebral blood flow autoregulation are that persons or animals with chronic hypertension can tolerate higher mean arterial pressures before an increase in cerebral blood flow occurs. This explains the clinical observation that many patients with chronic hypertension can tolerate mean arterial pressures that would cause severe symptoms in a previously normotensive person whose blood pressure has been acutely elevated. The mechanism of the protection of the blood brain barrier from disruption in chronic hypertension is unknown. It is possible that with chronic hypertension cerebrovascular hypertrophy leads to increased vascular resistance and inhibits an increase in cerebral blood flow at pressures that would usually cause an increase in flow. The fact that chronic hypertension can protect the blood brain barrier from disruption has been shown in rats by Mueller and Heistad (1980). The following figure 12 illustrates how the transfer of protein from the blood to the cerebral tissue was much less in chronically hypertensive animals than in normotensive controls.

Figure 12.



Protein transfer from the intravascular to extravascular space during acute hypertension. *p<0.05

It was felt that the decrease in permeability during acute hypertension in the chronically hypertensive animals was due to the hypertrophy of arteries and arterioles in these animals. However, the sympathetic nervous system has also been noted to have a protective effect against blood brain barrier disruption in hypertensive animals.

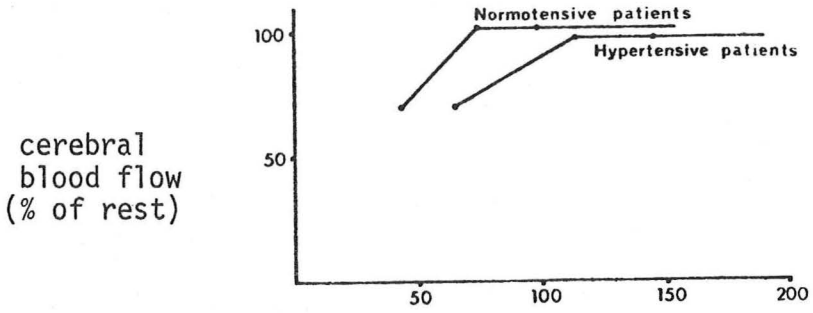
Studies by Mueller, et al, (1982) and Mueller and Ertel (1983) have suggested that an elevated sympathetic tone in young animals increases precapillary resistance during blood pressure elevation and leads to decreased capillary pressure and consequently protects against disruption of the blood brain barrier. In addition, chronic activity by the sympathetic nervous system enhances vascular hypertrophy which also increases precapillary resistance and protects against disruption of the blood brain barrier.

In summary a great deal of experimental evidence has accumulated in the past few years supporting the concept of forced vasodilatation with a subsequent increase in cerebral blood flow and disruption of the blood brain barrier as the principal pathogenic mechanism of hypertensive encephalopathy. However, theories of intensive vasospasm have not been disproven and further studies are needed to clarify the roles of vasospasm and vasodilatation in the pathogeneis of this clinical disorder.

THE EFFECTS OF ANTIHYPERTENSIVE AGENTS ON CEREBRAL BLOOD FLOW AUTOREGULATION

The shift of the cerebral blood flow autoregulatory curve to the right has important implications in the acute and chronic treatment of hypertension. Figure 13 summarizes the previously discussed data on the effects chronic hypertension has on the lower limit of autoregulation (Strangaard 1976).

Figure 13.

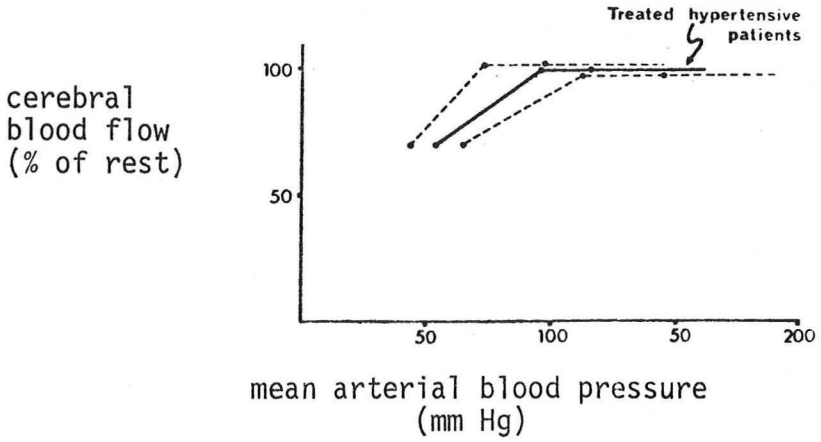


Mean cerebral blood flow autoregulation curves from normotensive and hypertensive patients (Standgaard, 1976).

This right ward shift has important clinical implications when the decision is made to acutely lower blood pressure in a hypertensive patient. These patients will reach the lower limit of autoregulation

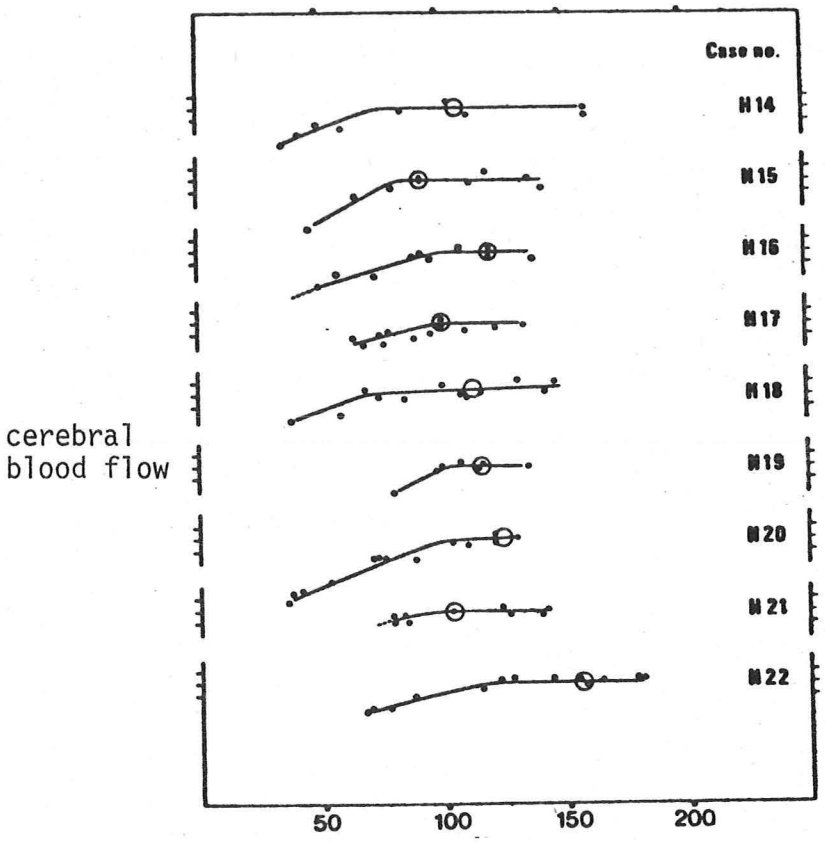
and subsequently suffer a fall in cerebral blood flow at mean arterial pressures that are tolerated easily by normotensive patients. This should not be used as an argument against the treatment of hypertension but illustrates the necessity for careful reduction of severe hypertension acutely to some level higher than normal.
The treatment of hypertension over a period of months probably causes a readaptation of cerebral blood flow autoregulation to a more normal curve. Figure 14 from Strandgaard (1976) illustrates the mean autoregulatory curve for nine patients with well controlled hypertension.

Figure 14.



This clearly illustrates that the mean autoregulatory curve tends to shift toward normal if hypertension is treated for a period of time. It must be noted, however, that the autoregulatory curves for hypertensive patients are extremely variable. This is illustrated in figure 15 from the same study.

Figure 15.



Individual curves of autoregulation of cerebral blood flow from nine patients with formerly severe hypertension, which at the time of the study was effectively controlled by antihypertensive treatment (Strandgaard, 1976).

In these nine patients the mean arterial pressure at which the lower limit of autoregulation was observed was extremely variable in that some patients had a curve that was almost normal while other patients had a lower limit of autoregulation that was similar to the curves of severe untreated hypertensive patients. This illustrates the need for careful observation of severely hypertensive patients when their blood pressure is lowered a significant amount.

The clinical implications of the shifts in the autoregulatory curves can be critical when designing an antihypertensive regimen for patients. In the above figure, the resting cerebral blood flow values in these patients were well above the lower limit of autoregulation

(noted by the open circles). However, if the lower limit of autoregulation is reached during hypotensive therapy a fall in global cerebral blood flow of about 30% will result in symptoms of cerebral hypoperfusion. Consequently, clinicians should be careful when treating severely hypertensive patients not to acutely lower the blood pressure to normal. Instead, the patient should be given a period of time for readaptation of the cerebral vessels to a normal blood pressure. Some patients, however, do not readapt their cerebral blood flow autoregulation during treatment with hypotensive agents. Although this group of patients cannot be identified before treatment is begun, clinicians should realize that some patients will continue to develop symptoms of cerebral hypoperfusion during hypotensive therapy even after blood pressure has been moderately controlled for several months.

The risk of lowering blood pressure below the limit of cerebral blood flow autoregulation should influence the clinician's choice of antihypertensive drugs and the rapidity that blood pressure is lowered. In certain clinical situations, i.e., hypertensive emergencies, patients with chronic hypertension should have their blood pressure lowered as rapidly as possible to a level above the observed lower limit of cerebral blood flow autoregulation in severe hypertension i.e., to a diastolic blood pressure of approximately 115 mm Hg. Patients with hypertension that has developed relatively acutely such as with toxemia of pregnancy or glomerulonephritis will usually tolerate blood pressure reduction to normal or near normal levels because their autoregulatory curve has not adapted to a higher level. Lowering blood pressure to a lower level risks inducing cerebral ischemia and border zone cerebral infarctions (Graham, 1975). In addition one should remember that any hypotensive regimen that does not block the sympathetic nervous system response to hypotension can cause reflex sympathetic vasoconstriction of the larger resistance vessels and lead to uneven perfusion or ischemia of the brain such as that seen with hemorrhagic hypotension (Fitch et al, 1975). Another consideration in choosing hypertensive therapy in severely hypertensive patients is the effect the drug chosen has on intracranial pressure. If during hypotensive therapy intracranial pressure rises to an unacceptable level, cerebral blood flow may be compromised and symptoms of cerebral ischemia may occur. This is especially true in patients with preexisting cerebral edema such as those with hypertensive encephalopathy. Finally, one should consider the possibility that drugs which directly dilate cerebral vessels can lead to uneven cerebral perfusion due to an intracerebral "steal", especially if the sympathetic nervous system is intact. Patients with atheromatous disease in intracranial or extracranial vessels may be at particular risk for complications from a fall in blood pressure and subsequent fall in cerebral blood flow in compromised areas, especially at border zones of arterial supply.

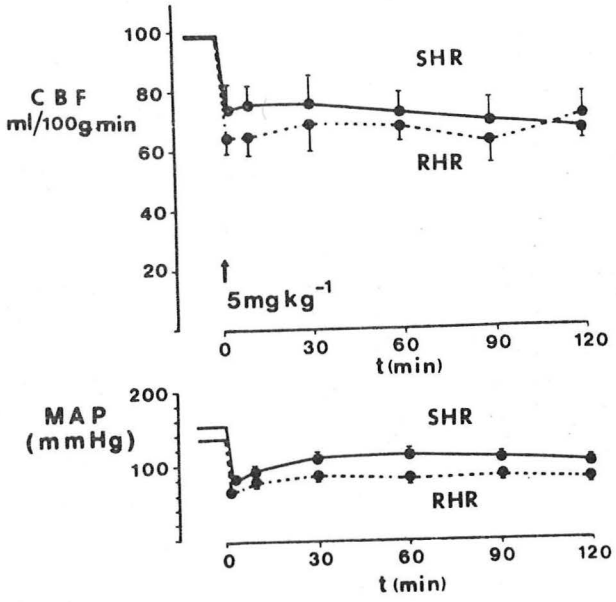
The effect of hypotensive drugs on cerebral blood flow in man has not been studied extensively because of the limitations inherent to measurements of cerebral blood flow. As expected most of the drugs studied have been parenteral agents used in the treatment of hypertensive emergencies.

Nitroprusside has been found to have variable effects on global and regional cerebral blood flow in patients despite its vasodilating properties which should cause an increase in flow (Candia, 1978). The fact that this increase in flow is not seen is probably due to a combination of factors. First, the sympathetic nervous system, if left intact, will attenuate the vasodilatation that would be expected from the drug alone. In addition, nitroprusside has been noted to cause an increase in intracranial pressure, an effect that limits any increase in cerebral blood flow. Also, the dose used is probably important in that lower doses tend to maintain or even increase cerebral blood flow while higher doses tend to decrease blood flow. This may be a function of dropping the blood pressure below the lower limit of autoregulation.

Hydralazine has been noted to cause an increase in cerebral blood flow when blood pressure is reduced (Overgaard and Skinhøj, 1975; Barry et al, 1984). In addition, hydralazine injected intravenously often causes an immediate increase in intracranial pressure probably due to dilatation of the intracranial vessels. Theoretically this combination of increased blood flow and increased intracranial pressure could lead to deleterious effects in patients who already suffer from cerebral edema (hypertensive encephalopathy).

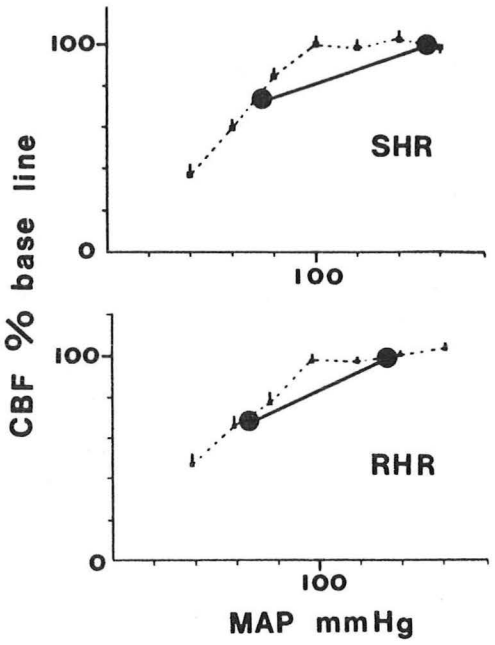
Diazoxide acts similarly to hydralazine; however, the intravenous injection of this drug into hypertensive animals results in no increase in cerebral blood flow. In fact, Barry, et al, (1983) found no effect on cerebral blood flow autoregulation by diazoxide. In this study cerebral blood flow fell as mean arterial pressure was lowered to normal with diazoxide as illustrated in figure 16.

Figure 16.



However, the fall in cerebral blood flow was no different than that obtained by hemorrhagic hypotension (figure 17).

Figure 17.



The cerebral blood flow fall induced by diazoxide (5mg/kg i.v.) in SHR and RHR is shown together with the corresponding autoregulation curve obtained by hemorrhagic hypotension.

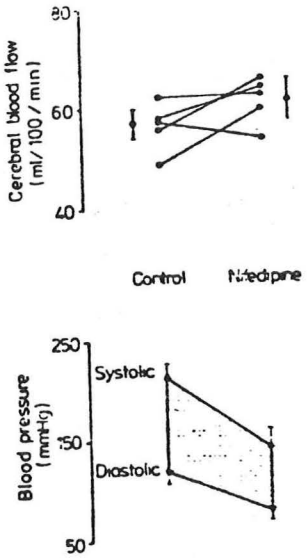
The authors concluded that diazoxide has little effect on cerebral vessels directly and autoregulation is left intact.

Trimethaphan has little effect on cerebral blood flow in doses up to 5 mg per minute (Olesen, 1973). In addition, it has been noted that hypotension induced by ganglionic blockade preserves cerebral blood flow autoregulation to a lower level than does hemorrhagic hypotension or hypotension induced by agents that leave the sympathetic nervous system intact. However, the side effects of ganglionic blockade and tachyphylaxis have limited its use significantly.

Nitroglycerin also has been used in patients with hypertensive emergencies, especially in patients with myocardial infarction and severe hypertension or in hypertensive patients during the immediate post coronary artery bypass surgery period. Although an increase in intracranial pressure and vasodilitation is seen with this drug cerebral blood flow is unchanged or increased (Hoffman, 1982).

Calcium channel blockers have recently gained wide attention as possible agents for use in hypertensive emergencies and urgencies due to their rapid onset of action as a vasodilator (Muller-Schweinitzer, 1983) and efficacy in rapidly lowering blood pressure to near normal levels (Magometschnigg, 1983). It has been postulated that the vasodilatating properties of this drug might allow blood pressure to be lowered to near normal levels without symptoms of cerebral ischemia. This has been studied in a few patients by Bertel, et al, (1983) who used this drug to treat several patients with hypertensive emergencies. These patients had a mean initial blood pressure of 221±22/126±14. After using oral nifedipine in a dose of 10 to 20 mg, blood pressure was lowered to 152±20/89±12 within 30 minutes without any clinical side effects. Despite the fall in blood pressure, a significant increase in mean global cerebral blood flow was noted in five patients.

Figure 18.



Effect of oral nifedipine on blood pressure and cerebral blood flow.

While this study appears to indicate that this vasodilator is well tolerated in patients with hypertensive emergencies caution must be exercised when using it to lower blood pressure in these patients. The posibility exists that nifedipine causes an intracranial "steal" just as has been postulated with other vasodilating agents. This has been suggested by Nobile-Orazio and Sterzi (1981) who reported two patients that developed symptoms of focal cerebral ischemia after blood pressure was lowered with nifedipine. Obviously further studies are needed

before this drug is widely used in the treatment of true hypertensive emergencies especially those with intracranial pathology.

Other drugs used in the treatment hypertension have been studied sporadically to determine their effects on cerebral blood flow. Traub, et al, (1982) have studied the effects of hydrochlorothiazide on cerebral blood flow in elderly patients with systolic hypertension. Average gray matter flow and cerebral vascular resistance was not significantly changed while blood pressure was lowered from 186/92 to 160/86 in fifteen elderly patients aged 61 to 76 years. It was concluded that cautious reduction in systolic blood pressure in elderly patients could be accomplished without impairment of cerebral perfusion.

Studies on the effect of methyldopa on cerebral blood flow have been inclusive. Meyer, et al, (1968) measured cerebral blood flow in hypertensive subjects and found an increase when patients with recent stroke were treated with methyldopa. However, changes in cerebral circulation due to the recent cerebrovascular events could have contributed to this increase. On the other hand Lavy, et al, (1980) showed that chronic administration of methyldopa to hypertensive patients for twelve weeks resulted in insignificant changes in cerebral blood flow. Probably the chronic administration of methyldopa has little effect on cerebral blood flow in healthy hypertensive patients.

Beta adrenergic blocking drugs administered acutely seem to depress cerebral blood flow (Agnoli et al, 1976; Hares et al, 1977). However, chronic administration of these drugs probably results in no significant change in global cerebral blood flow despite pharmacologic and hemodynamic differences in the drugs as illustrated in Table 2 from Griffith, et al, (1979).

Table 2.

	Cerebral blood flow ($ml\ 100\ g^{-1}\ min^{-1}$)	
	Pre-drug	On-drug
Labetalol (n=27)	45.1 (±1.1)	47.1 (±1.2)
Metoprolol (n=27)	45.5 (±1.0)	44.6 (±0.8)
Oxprenolol (n=27)	45.4 (±1.2)	46.7 (±1.3)
Sotalol (n=25)	45.6 (±1.0)	46.4 (±1.2)

The lack of a fall in cerebral blood flow with β-adrenergic blocking drugs is somewhat surprising in that these drugs generally cause an increase in vascular resistance due to the emergence of unopposed α-adrenergic activity. However, a recent study (Magnoni et al, 1973) reported a significant decrease in β-adrenergic receptor function in the cerebral vessels of hypertensive rats. This decrease may explain the lack of a rise in cerebrovascular resistance after beta blockade in the study by Griffith, et al, (1979).

The effect of prazosin on cerebral blood flow has been studied in a few hypertensive patients in which a small but significant increase occurred in cerebral blood flow following a single 1 mg dose of this drug when compared to placebo (Rutland et al, 1980).

Little is known about the effects of clonidine on cerebrovascular responses. Bertel, et al, (1983) reported several patients with various hypertensive emergencies who experienced a fall in global cerebral blood flow when given clonidine intravenously to lower blood pressure. Whether this was due to the fall in blood pressure or to alpha-adrenoreceptor induced vasoconstriction is unknown.

It is obvious that the invasiveness of accurate cerebral blood flow measurements has impaired the study of the effects that antihypertensive drugs have on the cerebral circulation. It is hoped that the recent development of noninvasive means to measure cerebral blood flow will greatly enhance our ability to study these drugs.

SPECIAL CONCERNS IN THE ELDERLY

Cerebral blood flow decreases with age as total gray matter mass declines. In addition, several disease processes are common in old age that affect cerebral blood flow thereby making this group especially susceptible to changes in cerebral blood flow that occur with antihypertensive treatment.

Atherosclerosis of the large cerebral vessels is a common problem in elderly patients. Because of pressure gradients that may be present

across these lesions, distal resistance vessels may be maximally dilated to maintain flow. A drop in systemic pressure could severely compromise the flow to the areas where the vessels are maximally dilated already. This obviously can lead to focal cerebral ischemia or stroke. Patients who have suffered a previous stroke have a decreased regional cerebral blood flow in the area of decreased metabolic activity and autoregulation probably does not exist in these areas. However, areas around the previous stroke may also have abnormal cerebral blood flow autoregulation which make these areas especially susceptible to further damage if blood pressure is lowered to an unacceptable level.

Diabetes mellitus causes vascular disease in the small and large vessels. Its effect on the function of small resistance vessels is unknown; however, the possibility that these vessels are affected by atherosclerosis may make the diabetic patient sensitive to the effects of aggressive antihypertensive therapy.

Dementia also is common in elderly patients with hypertension. In general, demented patients are found to have cerebral blood flows that are lower than normal persons (Simard et al, 1971).

Because of the above complicating factors any hypertensive therapy should be carefully monitored in elderly patients. Therapy should be aimed at gradual and careful reduction in blood pressure with special attention to symptoms of global or focal cerebral hypoperfusion, especially in patients with isolated systolic hypertension.

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