HYPERTENSIVE EMERGENCIES RECOGNITION AND MANAGEMENT

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HYPERTENSIVE EMERGENCIES

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Despite the large number of patients with chronic hypertension, hypertensive crisis constitutes a relatively rare medical emergency. However, marked and sudden elevation in blood pressure may represent an immediate threat to life. Prompt reduction of blood pressure in these situations is therefore essential and may be life-saving. In the majority of patients, hypertension progresses slowly and, if adequately controlled, seldom leads to a crisis. The consequences of severe elevation of blood pressure generally involve the brain, cardiovascular system and the kidneys. Therefore, rapid treatment of hypertension is necessary in order to prevent or reverse many of the morbid consequences. Any form of hypertension may lead to a crisis, the major determinant being the degree of blood pressure elevation rather than the etiology of the hypertensive state. Under certain circumstances, it is not only the degree of blood pressure elevation that determines the gravity of the clinical situation, but also the rate of rise in blood pressure, as exemplified by eclampsia and acute glomerulonephritis where hypertensive crisis can occur at blood pressures as low as 160/110 mm Hg (1). There are certain conditions that qualify as hypertensive emergencies, not so much because of the height of blood pressure elevation, but because of coexisting complications which make even moderate hypertension dangerous. These include acute left ventricular failure, intracerebral hemorrhage, acute dissection of the aorta, and coronary artery disease. Hypertensive emergencies rarely develop in previously normotensive persons and more commonly they occur in poorly controlled chronic hypertension. In previously normotensive individuals, acute elevations of blood pressure cause complications to a greater extent at any given level of blood pressure than in those with chronic hypertension (2).

In the management of hypertensive emergencies, prompt therapy takes precedence over diagnostic procedures and valuable time should not be wasted in the pursuit of an underlying etiology. The complications of hypertensive crisis are largely reversible, but the degree of reversibility critically depends on how soon the effective treatment is instituted.

For practical purposes and therapeutic priorities, I am categorizing hypertensive crises into <u>hypertensive emergencies</u> and <u>hypertensive urgencies.</u> Hypertensive emergencies (Table 1) are conditions with dire prognosis, in which delay of therapeutic intervention might potentially lead to irreversible sequelae, whereas, hypertensive urgencies are conditions with less serious immediate prognosis, but may ultimately lead to complications, if blood pressure is not aggressively treated. The examples of hypertensive urgencies are shown in Table 2.

Table 1

HYPERTENSIVE EMERGENCIES

1. Hypertensive encephalopathy
2. Acute aortic dissection
3. Pulmonary edema
4. Pheochromocytoma crisis
5. MAO inhibitor + tyramine interaction
6. Intracranial hemorrhage
7. Eclampsia

Table 2

HYPERTENSIVE URGENCIES

1. Hypertension associated with coronary artery disease
2. Accelerated hypertension
3. Severe hypertension in the kidney transplant patient
4. Postoperative hypertension
5. Uncontrolled hypertension in the patient who requires emergency surgery.

The syndrome of accelerated or malignant hypertension has been the subject of a recent Medical Grand Rounds (3), and therefore I have opted not to discuss this syndrome in great detail. My discussion will focus on other hypertensive emergencies.

MALIGNANT OR ACCELERATED HYPERTENSION

Definition. The term malignant or accelerated hypertension is usually applied to the hypertensive state that is associated with rapidly deteriorating blood pressure control and Grade III or IV Keith-Wagner retinopathy. No matter how severe the hypertension may be, it should not be classified as "malignant" unless papilledema is present. On the other hand, the term "accelerated" hypertension is characterized by the presence of hemorrhages or exudates in the retina.

Clinical Features. In malignant or accelerated hypertension, the sustained elevation of blood pressure is severe enough to cause damage to the vascular system. The vascular damage is clinically manifested as

neuroretinopathy or nephropathy. Malignant hypertension may develop during the course of essential hypertension, or sometimes as a manifestation of a secondary form of hypertension, particularly renal artery stenosis. The clinical features of malignant or accelerated hypertension are shown in Table 3.

Table 3

FEATURES OF ACCELERATED OR MALIGNANT HYPERTENSION

1. Marked elevation of diastolic BP
2. Malaise; Weight loss
3. Headache
4. Retinopathy
5. Renal failure (azotemia, proteinuria, hematuria, etc.)

More than 75% of patients with malignant hypertension have a previous history of blood pressure elevation, and in substantial numbers of these patients, there is also a strong positive family history of high blood pressure (4). The blood pressure in this condition is always high and is usually greater than 200/130 mm Hg. The patient may be entirely without symptoms, the condition being discovered by accident or the patient may present with clinical evidence of heart failure or renal insufficiency. Although some patients may be asymptomatic and free of complications, the majority of patients complain of headache which is most severe early in the morning. The consistent finding on physical examination of a patient with this condition is the presence of Grade III or IV retinopathy (Keith Wagner classification). The level of blood pressure, itself, while important, is not a major criterion for the diagnosis. Except for hypertensive encephalopathy, which will be described in detail subsequently, the symptoms of malignant hypertension are not distinctive. As alluded to previously, headache is common and can be sometimes very severe. Gross hematuria, weight loss, visual disturbance, generalized malaise and manifestations of secondary hyperaldosteronism (profound muscle weakness or paresthesias reflecting severe hypokalemia) are occasionally noted. The urinalysis usually reveals proteinuria or hematuria. As far as the blood chemistries are concerned, there is a certain degree of azotemia which can be severe sometimes, and anemia. The peripheral blood smear may reflect the evidence of intravascular hemolysis which is presumably secondary to mechanical destruction of the RBC's.

The characteristic pathological lesion of accelerated or malignant hypertension is fibrinoid arteriolar necrosis predominantly occurring in the kidneys, brain and retina (5,6). Although the pathogenesis of these

vascular changes has been debated for many years, there is convincing evidence for the importance of the absolute blood pressure level in the genesis of the vascular abnormalities (7). A possible role for the renin-angiotensin system has been evoked to explain the pathological changes in malignant hypertension (8), but this hypothesis has not been proven.

Prognosis. The prognosis of untreated malignant hypertension is extremely poor. Without adequate treatment more than 80% of patients succumb within 12 months (9-12) (Figure 1). The necrotizing arteriolitis of malignant hypertension is a rapidly progressive process that leads to irreversible renal failure if the process is uninterrupted, and therefore, the blood pressure should be urgently reduced to stop the necrotizing process and permit the damaged arterioles to heal. Modern antihypertensive therapy unquestionably has been shown to prolong life in patients with malignant hypertension (13-17), (Figure 2).

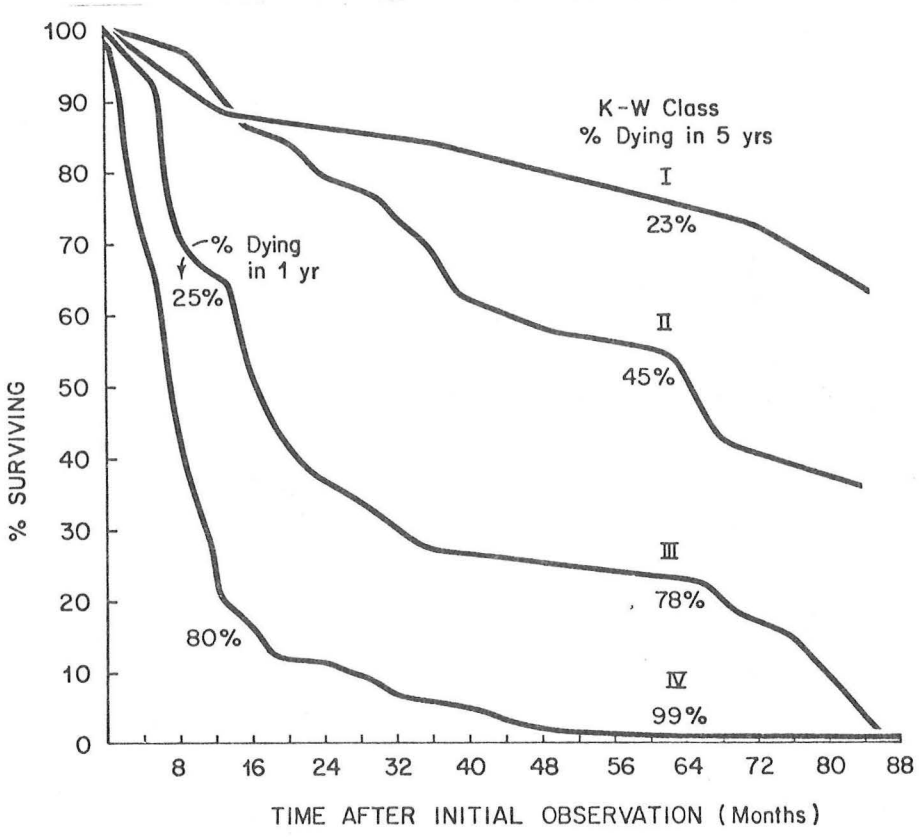


Figure 1: The prognosis of patients with different classes of retinopathy (Keith-Wagner), (Ref. 11)

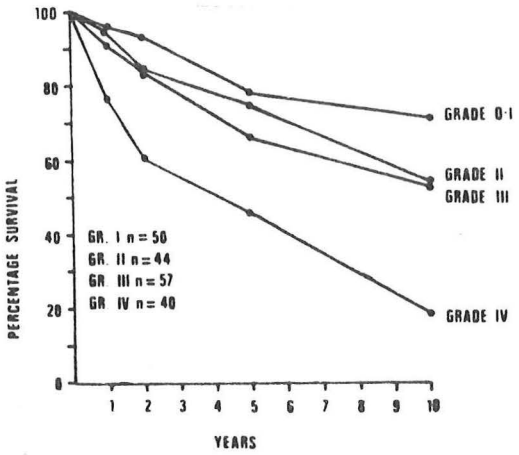


Figure 2: The percentage of hypertensives surviving with treatment for up to 10 years. (Barnett AJ, et al, Med J Aust 2:960, 1973).

Management. The patient with accelerated or malignant hypertension should be immediately hospitalized for intensive medical therapy. If the patient has a normal mental status and is able to take oral medications, intensive medical therapy should be instituted. The most useful oral agents for rapid control of blood pressure are the diuretics and direct vasodilators, such as hydralazine and the new agent, minoxidil. Since the direct vasodilators almost always cause reflexive increases in the heart rate and cardiac output, simultaneous administration of an adrenergic blocking agent to counteract these adverse hemodynamic effects is advisable. In some institutions, guanethidine loading is used to rapidly reduce the blood pressure but it is preferable to use a combination of a direct vasodilator and an adrenergic blocking agent. If the patient's condition is severe, or he is not able to take oral medications, the blood pressure can be reduced to the desired level by using one of the potent parenteral antihypertensive agents, such as diazoxide, sodium nitroprusside or trimethaphan.

Table 4

THERAPY OF ACCELERATED HYPERTENSION

1. Bedrest
2. Diuretics
3. Hydralazine or minoxidil
4. Adrenergic blocking agents

Parenteral Agents: Diazoxide, Nitroprusside or Trimethaphan

The advantage of sodium nitroprusside or trimethaphan is that the blood pressure control with these agents is smooth and can be tightly regulated, whereas with diazoxide, sometimes an exaggerated hypotensive reaction might ensue, particularly if the patient has been on antihypertensive agents previously. The parenteral drug of choice is sodium nitroprusside and the details of its clinical pharmacology and therapeutic use will be discussed later. The rapid institution of these antihypertensive measures usually arrests the vascular deterioration that constitutes the syndrome of accelerated or malignant hypertension. Once blood pressure control has been achieved and maintained to a satisfactory level, a detailed diagnostic evaluation may be undertaken if indicated by physical examination and/or laboratory findings. When the malignant hypertension is accompanied by cerebral, cardiac or renal complications, appropriate changes should be made in the choice of antihypertensive agents and the degree to which blood pressure is reduced should be modified. The clinical applications of the various parenteral antihypertensive drugs will be discussed in a later section.

HYPERTENSIVE ENCEPHALOPATHY

Hypertensive encephalopathy is a medical emergency caused by abrupt and severe elevation of blood pressure and represents the most serious complication of accelerated hypertension (18). The present rarity of this syndrome reflects overall improved management of hypertension. It is important to diagnose hypertensive encephalopathy promptly because rapid reduction of blood pressure results in the amelioration of the syndrome, which is otherwise potentially fatal. The syndrome of hypertensive encephalopathy was described as a distinct clinical pathological entity more than 50 years ago (19). The easy availability in recent years of potent antihypertensive agents has made the management of hypertensive encephalopathy much easier. Hypertensive encephalopathy occurs during the course of severe elevation of arterial blood pressure and is not limited to any specific etiologic type of hypertension although the syndrome tends to occur more commonly as a complication of acute glomerulonephritis, toxemia of pregnancy, and renal artery stenosis. In hypertensive encephalopathy, it is not only the absolute level but also the rapidity with which elevation of blood pressure occurs that determines the development of symptoms. They may appear at relatively low levels of blood pressure when hypertension is of recent onset. For example, it is not unusual to observe severe headaches, blurring of vision, and mental obtundation, characteristic of hypertensive encephalopathy, in children with acute glomerulonephritis or in women with eclampsia when the blood pressure is no greater than 160/100 mm Hg, whereas these symptoms rarely occur in chronic hypertensive patients until their blood pressure exceeds 240-250/150 mm Hg (20). Hypertensive encephalopathy occurs more frequently when hypertension is complicated by renal failure than when the kidney function is normal. At times, admittedly, it is difficult to determine how much of the cerebral symptomatology is due to uremia and how much is it due to elevation of blood pressure since the conditions may coexist.

Pathogenesis of Hypertensive Encephalopathy

Physiology of Cerebral Circulation. Normal cerebral blood flow remains relatively constant over a wide range of variations in systemic arterial blood pressure and has been determined to be 50 ml/minute/100 gram of brain tissue (21,22). This remarkable constancy of cerebral blood flow in the face of blood pressure fluctuations is accomplished by the process of cerebral autoregulation. By this process, with severe elevation of blood pressure, cerebral arterioles constrict and with any decrement in blood pressure, they dialate to ensure constant cerebral blood flow (Figure 3). The phenomenon occurs primarily at the small resistance cerebral arteries (23).

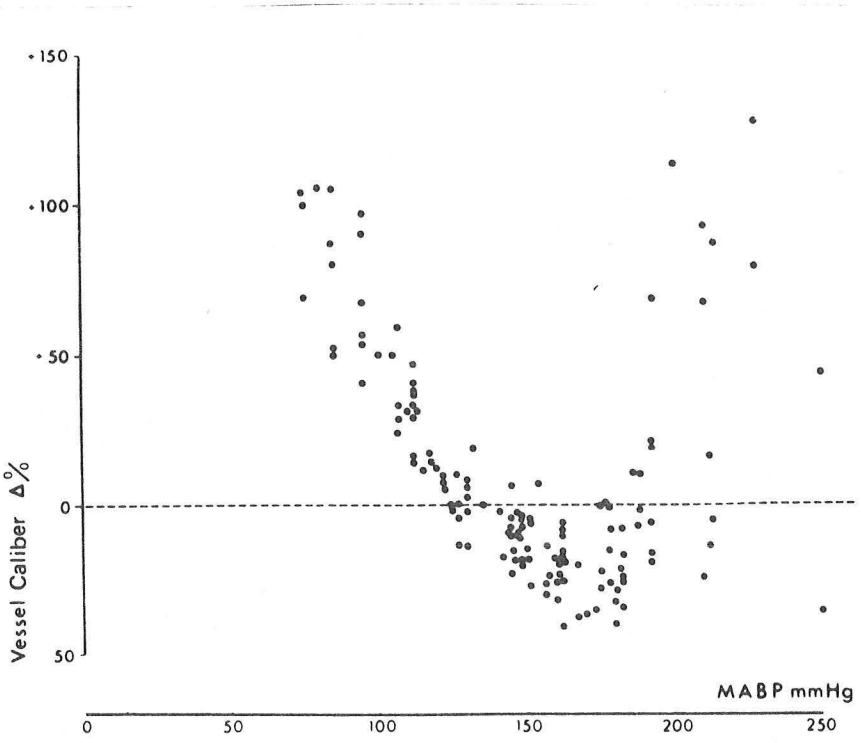


Figure 3: The observed changes in the caliber of pial arterioles in cats with variations in systemic blood pressure. (MacKenzie ET, et al. Circulation Research 39:33, 1976).

The precise nature of this autoregulatory mechanism has stirred much controversy and there is still disagreement although certain principles have gained general acceptance. The principal determinant of cerebral blood flow appears to be the blood pressure itself. The myogenic theory (24) proposes that altered tension of the vascular walls produced by the changes in blood pressure influences the inherent tone of the vascular smooth muscle, independent of the nervous mechanisms. The range of blood pressures over which autoregulatory responses are capable of maintaining adequate cerebral blood flow are shown in Figures 4 and 5.

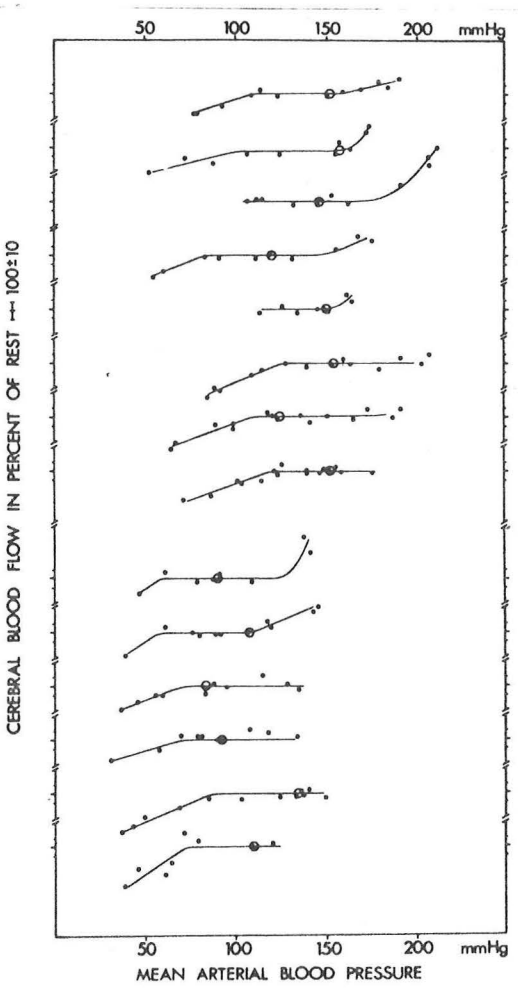


Figure 4: The curves of cerebral blood flow with varying levels of BP, the top 8 hypertensive, the bottom 6 normotensive. (Ref. No. 27)

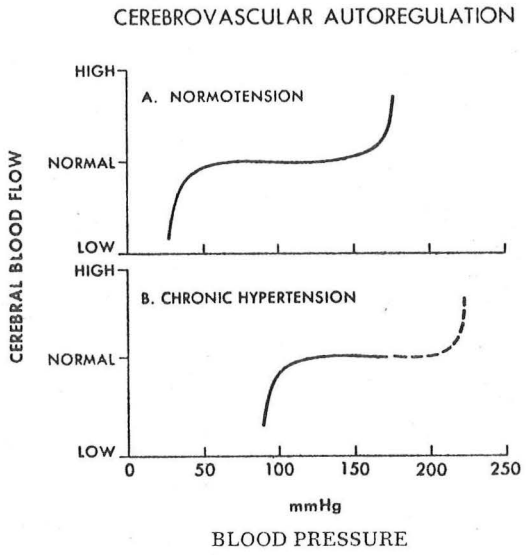


Figure 5: The relationship between cerebral blood flow and mean BP in normotensives (A) and in those with chronic hypertension (B).

In a normotensive individual, the lower limit at which autoregulation occurs is near the mean blood pressure of 60 mm Hg. As the blood pressure tends to fall below this level, even the maximum dilation of the vascular bed in the brain cannot compensate for the decreased perfusion pressure, and cerebral blood flow drastically declines. In contrast, when the blood pressure exceeds the upper limit of autoregulation, around 110 mm Hg, mean arterial cerebral blood pressure flow increases and encephalopathy develops (25). In chronically hypertensive patients, the lower limit of blood pressure for autoregulation is higher than it is in normal individuals. The shift of the upper limit of autoregulation in the hypertensives may be viewed as an adaptive mechanism allowing some degree of protection against further increments in blood pressure and explains why some patients tolerate extremely elevated blood pressures without developing encephalopathic crisis. The aforementioned observations, therefore, have important therapeutic implications guiding the degree of blood pressure reduction that should be achieved in chronically hypertensive individuals and previously normotensive individuals. Two theories have been proposed to explain the pathogenesis of hypertensive encephalopathy.

"Overregulation" or Arteriolar Spasm Theory. According to this theory, there is an exaggerated arteriolar, vasoconstrictive response to a rise in the blood pressure, resulting in overautoregulation with consequent reduction in cerebral blood flow resulting in ischemia, increased capillary permeability, rupture of capillary walls and ultimately, cerebral edema. This theory originally proposed by Oppenheimer and Fishberg (19) was subsequently confirmed by Byrom's classical

work on hypertensive encephalopathy (26). While experimenting with rats with renal hypertension, Byrom noted intense arterial spasm of cerebral blood vessels at the same time that the animals began to manifest cerebral symptoms, and this intense cerebral arteriolar spasm was followed by the appearance of cerebral edema. (Figure 6)

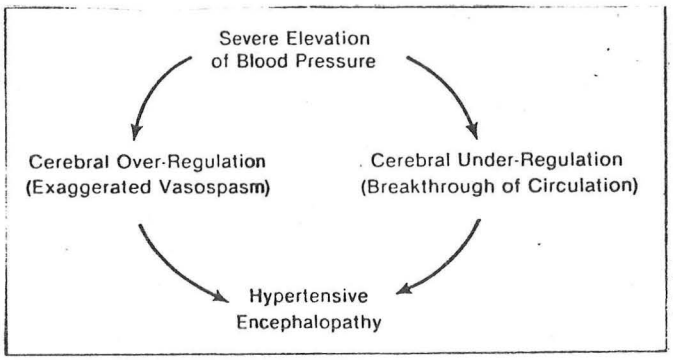


Figure 6: Pathogenesis of hypertensive encephalopathy. (Adapted from Ref. No. 28 A)

The "Breakthrough" or Failure of Autoregulation Theory. Recently, investigators have proposed an alternate hypothesis to explain the pathogenesis of hypertensive encephalopathy. They have suggested that under certain conditions, autoregulation fails to maintain constant cerebral blood flow and that "breakthrough" or "superperfusion" of cerebral circulation occurs when the blood pressure reaches certain upper limits (27,28). According to this theory then, severe elevation of blood pressure leads to decompensation or a breakthrough in cerebral blood flow with a consequent increase in the CBF that results in cerebral edema; what is meant is not merely an incomplete autoregulation, but actually a dilatation of cerebral blood vessels. Indeed, the question has been raised as to whether some of the supposedly narrowed segments suggested in the overregulation concept are indeed merely segments of normal diameter, whereas the true abnormalties reside in the dilated bead-like segments. It is also possible that despite the forced dilatation of certain segments of cerebral blood vessels, there might be foci of ischemia.

It is difficult to reconcile these divergent opinions. Fortunately, the treatment of hypertensive encephalopathy does not depend on the resolution of the controversy; rapid reduction in blood pressure results in amelioration of cerebral symptomatology and rational treatment does not rest on precise knowledge of the underlying mechanism. Clinical experience has shown that reduction of blood pressure to near normal levels is beneficial for patients with hypertensive encephalopathy. The only way to reverse the underlying process - whether there is excessive vasoconstriction or a breakthrough of circulation - is to reduce the blood pressure.

Clinical Features of Hypertensive Encephalopathy. The clinical features of hypertensive encephalopathy are usually precipitated by a sudden increase in blood pressure from a previous stable hypertensive level or by abrupt appearance of hypertension in a previously normotensive patient (i.e., toxemia of pregnancy or acute glomerulonephritis). In those previously hypertensive, the manifestations of hypertensive encephalopathy usually do not occur until the blood pressure exceeds about 250-260/150 mm Hg. Hypertensive encephalopathy may occur at much lower levels of BP when the onset of hypertension has been recent and abrupt. The onset of symptoms is usually subacute and although the exact time period of evolution of the syndrome has not been documented, it often takes 24 to 48 hours to develop a full-blown encephalopathy. The symptoms are listed in Table 5.

Table 5

SALIENT FEATURES OF HYPERTENSIVE ENCEPHALOPATHY

1. Marked elevation of BP
2. Headache
3. Nausea, vomiting
4. Papilledema*
5. Visual complaints
6. Focal transient neurological deficits (seizures)

Headache, usually severe and generalized, is present in most patients and is one of the common reasons why patients seek medical care. Although the relationship of arterial blood pressure to headache in essential hypertension has been disputed for many years, at least in hypertensive encephalopathy the headache seems directly attributable to elevation of blood pressure and reflects the development of cerebral edema. Visual complaints ranging from mild blurring to transient blindness are quite common. Nausea and vomiting (of a projectile nature) are the initial complaints in some patients. Focal or generalized convulsions occur in some. Convulsions appear to dominate the clinical picture in children with hypertensive encephalopathy (29). In others myoclonic twitches may be observed, but they are more likely to occur in uremic encephalopathy rather than hypertensive encephalopathy, *per se*. Focal cerebrovascular deficits such as transient hemiparesis and aphasia can punctuate the course of hypertensive encephalopathy, but it should be stressed that these neurological deficits are always transient and are not essential clinical features.

Hypertensive encephalopathy is also characterized by an alteration in the consciousness of the patient ranging from slight disorientation to ultimate coma if the condition progresses. Most patients with encephalopathy are restless and if the coma is present, it is usually not

so deep that the patient cannot be aroused. On examination of the patient as mentioned earlier, the blood pressure is usually markedly elevated. There is no arbitrary level of blood pressure at which point the encephalopathy is likely to occur. The spectrum of susceptibility to develop encephalopathy at varying blood pressures is a wide one and there are individual differences. The fundi usually reveal severe focal or generalized arteriolar spasm with exudates and/or hemorrhages. Bilateral papilledema is present in most patients but the syndrome has been known to occur in the absence of papilledema (30).

The cerebrospinal fluid is clear and may contain very few, if any, erythrocytes or leukocytes. The CSF pressure and protein content may be either normal or increased. Therefore, these studies are not helpful in making the diagnosis of hypertensive encephalopathy. The electroencephalogram may show transient focal disturbances or bilateral synchronous sharp and slow waves, but again, these abnormal EEG findings are nonspecific and do not provide sufficient help in making the diagnosis of hypertensive encephalopathy. The skull x-rays, brain scan and echoencephalogram are within normal limits. Although not helpful to diagnose the encephalopathy, these findings are important in ruling out other intracranial disorders. Whenever there is doubt about the diagnosis, one should not hesitate to perform a lumbar puncture to rule out other conditions. The best and the only reliable clinical criterion for confirming the diagnosis of hypertensive encephalopathy is the prompt response to hypotensive therapy and if this does not occur, then the diagnosis should be questioned.

In none of the conditions with which hypertensive encephalopathy may be confused do the clinical features abate so promptly after reducing the blood pressure. The headache and focal neurological deficits and the sensorium often clear dramatically, sometimes within 60 minutes after the reduction of blood pressure. Recovery may be somewhat slower in patients who are uremic or whose symptoms have been present for many hours before antipressor therapy. The funduscopic abnormalities may resolve much slower than the improvement in the general status of the patient.

Differential Diagnosis. When a patient presents with severe headache, papilledema, altered mental status and severe hypertension, the most likely diagnosis is hypertensive encephalopathy unless proven otherwise. The only definitive criterion, however, for confirming the diagnosis is prompt response of the patient's condition to antihypertensive therapy. The antecendent increase in blood pressure, often to very high levels, the severe headache, followed by subacute alteration in conscious state and variable, transient and often minimal neurological deficits should serve to differentiate hypertensive encephalopathy from some of the other clinical conditions with which it is likely to be confused, such as intracranial hemorrhage, cerebral infarction, brain trauma. The important clinical features in the differential diagnosis of hypertensive encephalopathy are shown in Tables 6 and 6A.

Table 6: Features of Hypertensive Encephalopathy and Other Intracranial Disorders

	EVOLUTION	HEADACHE	CONSCIOUSNESS	SIGNS
HYPERTENSIVE ENCEPHALOPATHY	SUBACUTE (12-48 HRS)	SEVERE GENERALIZED RECENT ONSET	INITIALLY CLEAR BUT PROGRESSES TO COMA	NAUSEA & VOMITING VISUAL DISTURBANCE SEIZURES TRANSIENT NEUROLOGICAL DEFICITS
CEREBRAL INFARCTION	RAPID (FEW MIN. TO 6 HRS)	NONE OR MILD	INATTENTIVE COMA VERY RARE	FIXED NEUROLOGICAL DEFICITS
CEREBRAL EMBOLUS	SUDDEN	NONE OR MILD	MILD LETHARGY	CHANGING SIGNS
CEREBRAL HEMORRHAGE	RAPID	SUDDEN SEVERE OCCIPITAL	RAPID PROGRESSION TO COMA	DENSE DEFICITS
SUBARACHNOID HEMORRHAGE	RAPID	SUDDEN SEVERE LOCAL TO GENERAL	NORMAL OR ALTERED DEPENDING ON THE SITE & SECONDARY INVOLVEMENT	FEVER STIFF NECK APHASIA CRANIAL NERVE PALSIES

Table 6A:

DIFFERENTIAL DIAGNOSIS OF HYPERTENSIVE ENCEPHALOPATHY

	CSF PRESSURE	CSF PROTEIN	CSF CELLS
HYPERTENSIVE ENCEPHALOPATHY	N OR ↑	N OR ↑	0
CEREBRAL INFARCTION	INITIALLY NORMAL MAY ↑ IN 2-3 DAYS	N OR ↑	VARIABLE
CEREBRAL EMBOLUS	INITIALLY NORMAL MAY ↑ IN 2-3 DAYS	N OR ↑	FEW RBC ± XANTHOCHROMIA
CEREBRAL HEMORRHAGE	↑↑	USUALLY ↑	BLOODY +
SUBARACHNOID HEMORRHAGE	↑	↑↑	BLOODY +++

Since hypertensive encephalopathy is likely to be confused with certain intracranial structural lesions, one should do a meticulous evaluation of the patient. Unfortunately, it is not easy to obtain details of the history from a stuperous patient. Hypertensive encephalopathy may indeed be the first manifestation of hypertension in patients who have not had their blood pressure measured for several years. This condition must be distinguished from cerebral infarction or hemorrhages and uremic encephalopathy. In one series (31), 24 of 42 patients who were thought to have hypertensive encephalopathy were later found to have either cerebral infarction, hemorrhage or uremic encephalopathy.

The differential diagnosis should include the possibilities of an intracranial mass lesion, seizure disorder and meningitis - all of which may incidentally coexist with severe hypertension (Table 7).

Table 7

DIFFERENTIAL DIAGNOSIS OF HYPERTENSIVE ENCEPHALOPATHY

1. Acute cerebrovascular accidents
2. Uremic encephalopathy
3. Benign intracranial hypertension
4. Intracranial mass lesion
5. Seizure disorder

One should also consider possibility of a reflex elevation of the systemic arterial blood pressure as the result of ischemia of the brain. There are said to be certain intrinsic mechanisms in the brain stem which, when rendered ischemic, reflexly elevate the systemic blood pressure as a protective phenomenon (32). The possibility that systemic blood pressure can be a protective phenomenon under certain ischemic conditions of the brain stem, remains an attractive one, and may indeed prove to be an explanation for some cases of hypertension following cerebral ischemia. There is no conclusive evidence to demonstrate the definite cause-effect relationship between the ischemia of brain tissue and consequent increase in systemic blood pressure.

Management of Hypertensive Encephalopathy. Once the diagnosis of hypertensive encephalopathy seems likely on the basis of constellation of clinical findings that have been discussed, the blood pressure should be lowered to near normal levels. The patient with encephalopathy should be ideally managed in an intensive care unit with constant monitoring of the vital signs. The most important aspect of therapy is to reduce the blood pressure rapidly to near normal levels. Although Strandgaard, et al. (27) warned that cerebral blood flow may be jeopardized

by rapid lowering of blood pressure to normal levels in chronically hypertensive patients, with smooth reduction in BP, one can avoid the hypotensive sequelae. The presently available parenteral hypotensive drugs produce prompt and dramatic relief of symptoms of hypertensive encephalopathy.

There are several potent hypotensive agents that can be used in this situation which are listed in Table No. 8. Although sodium nitroprusside, diazoxide and trimethaphan are all effective and rapidly acting agents, sodium nitroprusside or diazoxide should be chosen. Because of the smoothness with which it lowers the blood pressure with rapid onset and offset of action, sodium nitroprusside is preferred over diazoxide in several institutions. These drugs are discussed in detail elsewhere.

Table 8

DRUGS FOR THE TREATMENT OF SEVERE HYPERTENSION

NITROPRUSSIDE

DIAZOXIDE

TRIMETHAPHAN

HYDRALAZINE

Hydralazine hydrochloride, a direct vasodilating agent has been successfully used in the treatment of hypertensive emergencies for several years. Although effective in appropriate doses, its use in hypertensive encephalopathy has now been largely supplanted by the more potent drugs that will be discussed. Clonidine hydrochloride, methyldopa and reserpine should not be used for the treatment of hypertensive encephalopathy because of their delayed action and direct effects on the central nervous system, which may make it difficult to monitor the patient's progress. Convulsions that occur during the course of hypertensive encephalopathy are usually terminated with the reduction of blood pressure itself, but occasionally anticonvulsive therapy may be required. Once the encephalopathic crisis has fully resolved and the patient is able to take oral medications, appropriate antihypertensive therapy must be begun.

Summary

Although it is sometimes difficult to distinguish hypertensive encephalopathy from other cerebral complications of severe hypertension, the *sine qua non* of hypertensive encephalopathy is its prompt response to antihypertensive therapy. Nitroprusside and diazoxide are the drugs of choice whereas several untoward effects make trimethaphan a less desirable treatment choice. If the patient's neurological syndrome does not improve or worsens with therapy, alternate diagnosis should be immediately sought. The physician should also probe for possible factors responsible for precipitous elevation of blood pressure, such as reasons for cessation of drug therapy or possible onset or progression of renal artery stenosis, and suitable steps should be taken to prevent the recurrence of the syndrome. There are few medical emergencies in which objective response to therapy is so readily apparent as in hypertensive encephalopathy.

HYPERTENSIVE ENCEPHALOPATHY

CHOOSE – SODIUM NITROPRUSSIDE
DIAZOXIDE
TRIMETHAPHAN
HYDRALAZINE

AVOID – METHYLDOPA
CLONIDINE
RESERPINE

HYPERTENSION ASSOCIATED WITH CEREBROVASCULAR ACCIDENT

Whereas there is good evidence that control of hypertension reduces the incidence of both intracranial hemorrhage and thrombotic strokes, a patient who presents with severe hypertension during an acute cerebral vascular accident presents a difficult problem. Many, but not all physicians, recommend reduction of blood pressure with parenteral administration of hypotensive drugs. The cerebral arterial perfusion pressure depends on the difference between the systemic arterial pressure and the intracerebral pressure. With increased intracerebral pressure, the autoregulation curve or the relationship between the systemic blood pressure and the cerebral blood flow becomes unpredictable (33). The goal of treatment in the treatment of severe hypertension associated with cerebral vascular accidents is to lower the blood pressure without depressing the mental functions which may compound the interpretation of the neurological status. Therefore, agents with rapid onset, but short duration of action are preferred so that the hypotension can be reversed if there is worsening of the neurological status. Unfortunately, there are no data in the literature that will guide the practicing physicians about the standard approach to managing these patients. The therapy should be strictly individualized, depending on the patient's condition and coexisting cardiovascular and neurological status.

Is the Treatment Harmful? Important theoretical objections to decreasing the blood pressure have been raised on several grounds. First, in the area for cerebral infarction, there is maximal vasodilatation and loss of autoregulatory function. Blood flow to the area of marginal ischemia, therefore, depends on blood pressure itself and any further decrements in blood pressure may further compromise the blood flow to an ischemic zone. Secondly, when the intracranial pressure is increased, there is a reflex increase in the blood pressure, the so-called Cushing's reflex (34). In such circumstances, the decrease in systemic blood pressure may result in a sharp reduction in cerebral blood flow and further compromise cerebral dysfunction. Thirdly, after the development of intracranial hemorrhage, vasospasm may develop. A sustained blood pressure increase may therefore be needed to overcome this increase in the resistance. All of these objections are mostly theoretical and the harmful effects of decreasing the blood pressure in cerebrovascular accidents have been largely anecdotal since there are no large scale controlled studies to guide the appropriate therapeutic approach.

Is the Treatment of Hypertension Beneficial? Intracerebral hemorrhage is a devastating complication of chronic hypertension with a mortality as high as 84% in one month (35). In such a catastrophic illness, it will be difficult to find meaningful statistics showing the benefit or lack of it from immediate antihypertensive therapy. A survey

of 45 prominent neurologists from the United States and England (36) showed that 89% would favor acute antihypertensive treatment in such patients in the hope of preventing further hemorrhage. In one study (37), there was a significant benefit of antihypertensive therapy in managing hypertensive cerebral hemorrhage (Tables 9 and 10). Unfortunately, it was not mentioned with what rapidity and to what degree the blood pressure was lowered in these patients. Although the data are very limited because of the study design and incomplete patient details, the authors have concluded that medical treatment in the acute phase of intracranial hemorrhage is advisable, especially if the blood pressure is elevated at the time of admission to the hospital.

Table 9: Effects of Antihypertensive Treatment in Massive Stroke (Ref. 37)

HYPERTENSIVE CEREBRAL HEMORRHAGE

(PATIENTS COMATOSE*)

	TOTAL	ALIVE		DEAD	
TREATMENT		NO.	%	NO.	%
ADEQUATE	29	7	24	22	76
INADEQUATE	65	5	8	60	92
NONE	41	0	0	41	100

Table 10: Effects of Antihypertensive Treatment in Stroke, (Patients Awake) (Ref. 37)

HYPERTENSIVE CEREBRAL HEMORRHAGE

(PATIENTS AWAKE*)

	TOTAL	ALIVE		DEAD	
TREATMENT		NO.	%	NO.	%
ADEQUATE	11	8	73	3	27
INADEQUATE	18	10	55	8	45
NONE	3	1	33	2	67

In contrast to the intracerebral hemorrhage where medical management is indicated, the treatment of intracerebellar hemorrhages is somewhat different. In this condition, surgical decompression of the cerebellar hematoma is indicated and in most cases is life-saving. Thus, with the present state of our knowledge, no specific guidelines can be given about the management of hypertensive crises occurring in patients with cerebrovascular accidents. However, based on the pathogenesis of these conditions, especially intracerebral hemorrhage and possibly subarachnoid hemorrhage, if the patient has severe hypertension, it is advisable to reduce the blood pressure to near normal levels or to the degree which will not compromise the cerebral function. However, if there is evidence of progression of the disease or worsening of the neurological manifestations, then one has to reassess this therapeutic approach. Appropriate precautions should be taken to avoid hypotension in these patients and it is advisable not to lower the diastolic blood pressure to less than 110 mm Hg usually. Such a smooth, desired level of blood pressure control is only achieved with either sodium nitroprusside or trimethaphan. Because of the unpredictable responses that might occur with diazoxide, this agent is best avoided in this situation.

Table 11

INTRACRANIAL HEMORRHAGE

CHOOSE –	NITROPRUSSIDE
	TRIMETHAPHAN
AVOID –	DIAZOXIDE
	HYDRALAZINE

ACUTE AORTIC DISSECTION

"There is no disease more conducive to clinical humility than aneurysm of the aorta"

---Sir William Osler

The occurrence of dissecting aortic aneurysms in patients with hypertension and the frequent presence of hypertension in patients with dissecting aneurysm of the aorta are well-established (38). Dissection of the aorta is the most common acute disease of the aorta and probably occurs at the rate of around five to ten cases per million population each year. In addition to being the most common catastrophe involving the aorta, the acute dissection is also the most lethal, as illustrated in Figure 7.

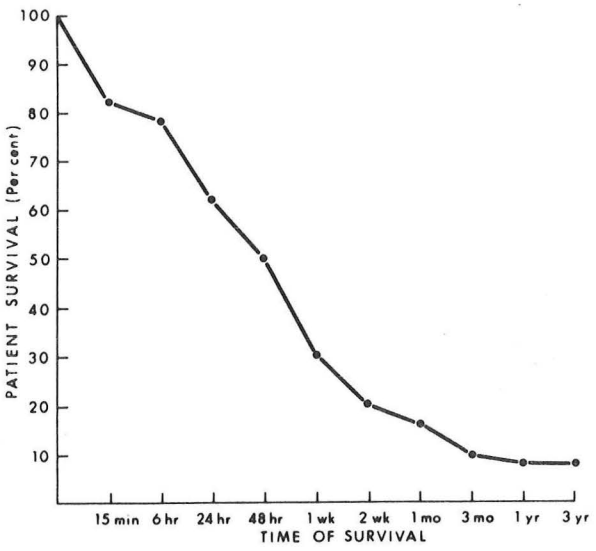


Figure 7: Length of survival of 963 patients with untreated acute aortic dissection (Agnostopoulos CE, et al., Am. J. Cardiol. 30:263, 1972)

As evident, the mortality rate is approximately 22% at six hours, 28% at 24 hours and half the patients are dead within 48 hours if left untreated. After one week, 70% of the patients have died and after three months, 90%. Of those eight to ten percent who survive three months, essentially all of them will continue to survive for the next one to three years. Approximately 90% of patients will either be hypertensive when seen upon admission to the hospital or have a history of hypertension.

Over the past 30 years or so, remarkable advances in the diagnosis and therapy have improved the survival of patients with acute aortic dissection. The mortality of the aortic dissection results not from the intimal tear by itself, but rather from the course taken by the dissecting hematoma which may rupture anywhere along the aorta, most commonly into the pleural or the pericardial space or may obliterate the blood supply to a major organ. Therefore, the therapeutic maneuvers must be directed toward the latent period between the intimal tear and death in order to arrest the usual progression of the disease.

Pathophysiology. One of the earliest recorded cases of aortic dissection was of King George II of England whose autopsy findings were described in a 1762 issue of The Philosophical Transactions of the Royal Society of London which stated the following:

> *"In the trunk of the aorta, we found a transverse fissure on its inner side about an inch and one-half long through which some blood has recently passed under its external coat and formed an elevated eccymosis. This appearance shewed the true state of an incipient aneurysm of the aorta."*

The two centuries following his majesty's death witnessed the evolution of the basic understanding of the pathological features of this devastating disease. These include the incrimination of the medial wall of the aorta as the primary site of the disease, the documentation of clinical findings and eventually the proposal of the presently accepted pathological concept of cystic medical necrosis, the lesion that predisposes to dissection (39). The disruption of the intima is likely to occur in those portions of the thoracic aorta that are subject to the greatest stress, namely, the ascending aorta and the portion of the descending aorta just beyond the origin of the left subclavian artery. Thus, when the intima is torn, each systole thrusts blood into the aortic wall creating a false lumen between the intima and the media. So, when the blood continues to enter the aortic wall, it progresses distally resulting in a double barreled aorta. The situations that contribute the development of medial necrosis are listed in Table 12.

Table 12

FACTORS CAUSING MEDIAL NECROSIS

1. Disrupted maintenance of the aortic caliber - atherosclerosis - cholesterol deposits.
2. Obstruction to the outflow - hypertension, coarctation, etc.
3. Hyperfunction of the cardiac pump - hyperkinetic state.
4. Hypervolemia - too much volume entering a small tube. - Pregnancy.
5. Destructive interference - trauma
6. Inherent abnormalities of the aortic structure such as Marfan's syndrome and lathyrism.

The above factors are known to contribute to the development of medial necrosis, however, certain mechanical factors will be needed to complete the dissection process. The mechanical factors leading to dissection are listed in the following table.

Table 13

FACTORS KNOWN TO LEAD TO THE ULTIMATE BREAKING OF THE INTIMA

1. Pulsatile flow and rate
2. Shearing and friction
3. Turbulence and viscosity
4. Suction on the intima
5. Systolic thinness

The two most useful classifications of dissection of the aorta are shown in the following tables. The anatomical type was first described by DeBakey (40) and in more recent years, a modified therapeutic classification was proposed by Anagnostopoulos (41).

Table 14

DEBAKEY'S CLASSIFICATION OF DISSECTING ANEURYSMS

1.	Type 1	Begins in the ascending aorta and extends at least into the arch and possibly through the descending aorta.
2.	Type 2	Dissection is localized to the ascending aorta only.
3.	Type 3	Begins in the descending aorta. Sometimes a Type 3 dissection may have a retrograde progression through the arch and may even dissect into the pericardium.

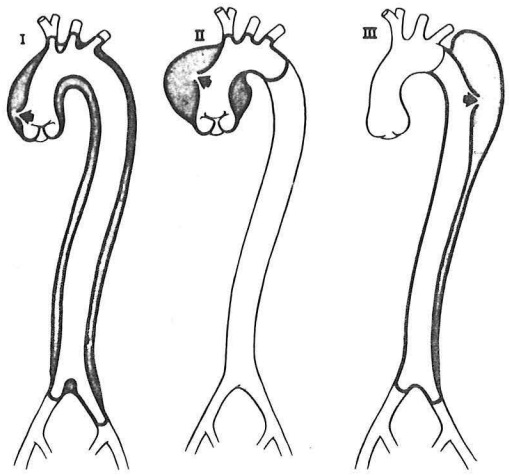


Figure 7A: DeBakey's Classification of Dissecting Aneurysms

Table 15

THE NEW ABC THERAPEUTIC CLASSIFICATION

Class A involves the ascending aorta
A1 with complications A2 without complications

Class B dissections do not involve the ascending aorta
B1 with complications B2 without complications

Class C inoperable

Class A1 The therapeutic modality of choice is surgery, preceded by stabilization of the patient by medical means.

Class A2 Medical treatment followed by surgery at a later time.

Class B1 Also requires surgery, but the patient has to be stabilized by medical treatment.

Class B2 Mostly medical, only in certain situations is elective surgery indicated.

Class C Inoperable and therefore, medical therapy is intensified.

Clinical Features. The dissecting aortic aneurysms afflict men more frequently than women with a peak incidence around the sixth decade, although patients with Types 1 and 2 dissection are on the average, somewhat younger. The usual patient with a dissection of the aorta, especially involving the ascending aorta, is the elderly male with a chronic history of hypertension who presents with severe and persistent chest pain. The symptoms of acute dissection are listed in the following table.

Table 16

CLINICAL FEATURES OF ACUTE AORTIC DISSECTION

1. Severe pain in the chest,intrascapular region, neck, midback, sacral area
2. Syncope
3. Confusional state or headache
4. Blindness
5. Hemoptysis
6. Dyspnea
7. Nausea and vomiting
8. Melena or hematemesis
9. Oliguria, anuria or hematuria
10. Paralysis

Of all the symptoms that have been listed, severe pain is the most important manifestation of acute dissection. It is easily confused with the pain of acute myocardial infarction. There are certain subtle qualitative differences between the pain of aortic dissection and myocardial infarction. The pain of dissection is abrupt in onset and is quite severe right from the onset, whereas patients with acute myocardial infarction rarely report that the pain began abruptly. The pain of myocardial infarction may wax and wane, whereas the aortic dissection pain occurs abruptly and persists. Although the patient's description of the pain may not indicate the site of dissection, it might sometimes reflect the extent of dissection. It is the quality of pain rather than its precise location that characterizes the patient with acute aortic dissection. Certain terms, such as tearing, lacerating, throbbing, ripping, excruciating and burning have been used by patients with acute dissections (42,43). The onset of pain is almost always sudden and is unremitting in most patients and the fear of death is imminent. Frequently, the onset of pain is not preceded by any special activity and many patients wake up with acute pain.

The localization of pain is variable. Since in many cases the entire thoracic aorta or parts of the abdominal aorta are involved, a spectrum of presentations is seen. It may occur in the anterior midchest or in the left side of the chest in the submental region, substernal region, facial and intrascapular areas or in the midback or even

in the sacral areas with radiation to the involved extremities. Hence, the onset of any severe pain should be suspect and the possibility of acute aortic dissection should be entertained in the differential diagnosis. The pain of dissection sometimes suggests the extent of the dissecting process. For example, with pain in the flank, one should think about the possibility of the dissection involving the renal arteries, whereas, pleuritic pain is evidence for a dissection of the descending aorta. Severe epigastric pain as a presenting manifestation may be confused with acute peritonitis. Signs such as sudden pulselessness in an extremity or sudden appearance of a diastolic murmur together with appearance of such severe pain should alert the physician to the possibility of a dissection. Following the resolution of the initial attack, recurrence of pain may signify resumption of the dissection process.

Dyspnea, orthopnea, hemoptysis are sometimes the presenting features of acute dissection. Tracheal compression, hemothorax, acute aortic insufficiency and pericardial tamponade may also be seen. Neurological symptoms such as syncope, although uncommon, reflect transient cerebral ischemia secondary to compression of the origin of the carotid and innominate blood vessels. Headache, confusion, or syncope were present in 26% of the patients in one series (42). Transient blindness has also been reported. Any of these neurological symptoms suggest an aortic dissection in contradistinction to acute myocardial infarction.

Gastrointestinal symptoms such as epigastric pain, nausea, vomiting, hematemesis or melena may be the result of ischemic gastrointestinal dilatation; the occurrence of hematemesis or melena heralds an ominous prognosis (42). Genitourinary symptoms such as oliguria, hematuria or anuria occur if the dissection involves the renal vasculature and are reversible with proper treatment.

Physical Findings in Acute Dissection. The physical findings of acute dissection are listed in the following table.

Table 17

PHYSICAL FINDINGS OF ACUTE DISSECTION

1. Hypertension
2. Tachycardia or bradycardia
3. Shocky appearance
4. Rales
5. Deficiency of pulses
6. Cardiac tamponade
7. Unilateral or bilateral jugular venous distention
8. Cardiomegaly
9. Hemothorax
10. Pericardial friction rub
11. Physical findings of aortic insufficiency
12. Hemiplegia, paraplegia
13. Facial paralysis
14. Paralytic ileus

About 90% of patients with acute aortic dissection have either hypertension at the presentation or a history of chronic hypertension. The pulse deficits which are found in about half of the patients with proximal dissection are an important clue to the diagnosis of acute aortic dissection. The murmur of acute aortic regurgitation is a finding that is quite common in patients with proximal dissection, occurring in more than 50%. The mechanisms of aortic regurgitation in the dissecting aortic aneurysm are shown in Figure 8. Examination of the neck sometimes reveals jugular venous distention from obstruction secondary to an expanding hematoma around the aorta or from cardiac tamponade. The pulsating neck mass may indicate a forward extension of dissection. Cardiomegaly is a common finding in many patients with this condition and reflects the hypertensive heart disease. The pleural effusion, if present, is always bloody and on the left side, a result of leakage through adventitial tears.

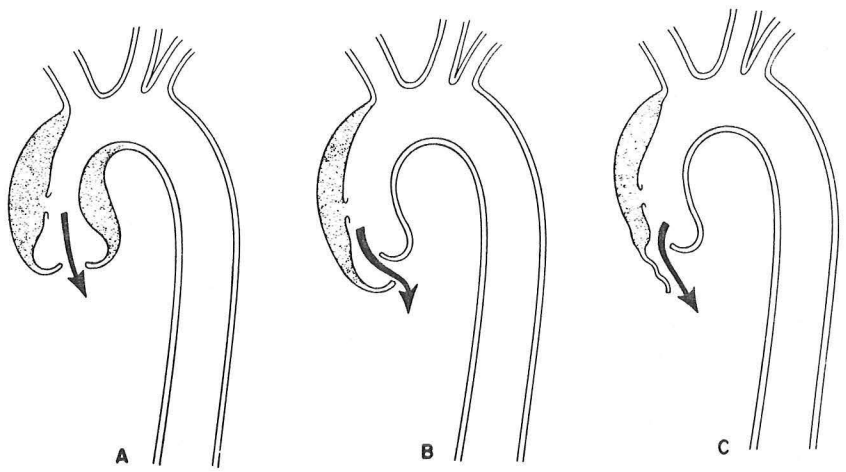


Figure 8: Mechanisms of aortic regurgitation in dissecting aortic aneurysms.

The other findings which occur in dissection of the aorta are: reduplicated pulses, a pulsatile sternoclavicular joint, Horner's syndrome caused by compression of the cervical sympathetic ganglion, vocal cord paralysis and hoarseness resulting from pressure on the left recurrent laryngeal nerve and heart block as a result of dissection retrograde into the intraatrial septum (45).

Laboratory Findings. Except for chest x-ray and angiography, the laboratory is of little help in making the diagnosis of dissecting aneurysm. The electrocardiogram is useful in a negative sense, to rule out the possibility of an acute myocardial infarction. Left ventricular hypertrophy is common and the cardiac enzymes are usually normal or sometimes the LDH may be elevated due to hemolysis within the false channel.

Echocardiography. Echocardiography has been found to be of value in the diagnosis of proximal aortic dissections and also may help demonstrate the presence of aortic regurgitation (46,47), (Figure 9). Although there are no large scale data from gated blood pool scanning, the technique also may demonstrate the location of the aneurysm. The x-ray findings in dissection are listed in the following table.

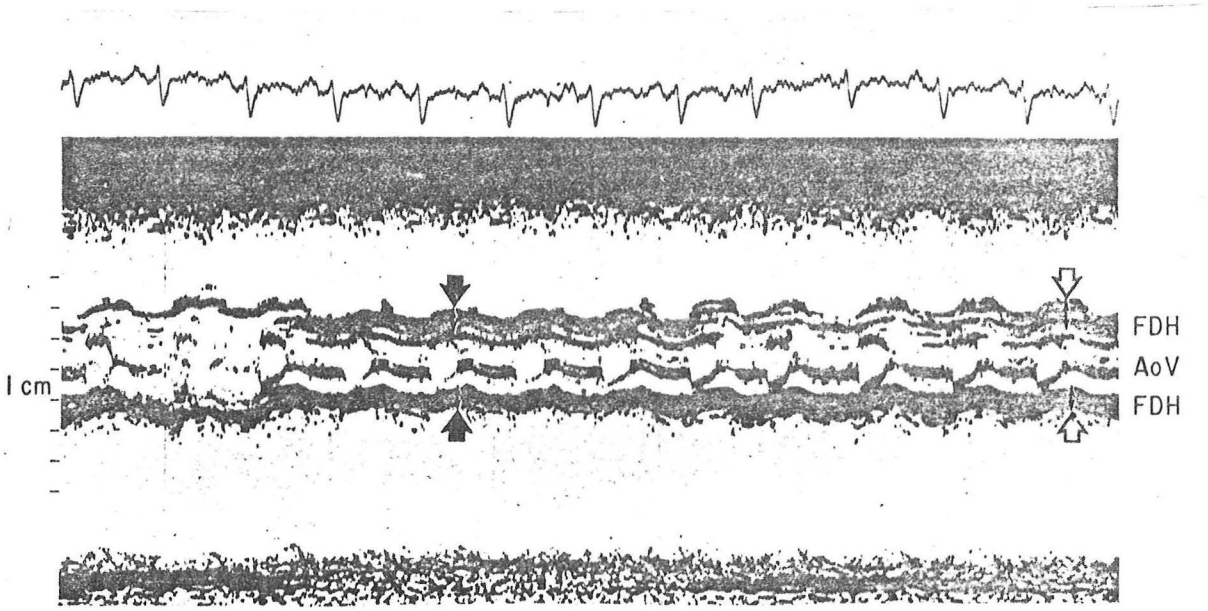


Figure 9: Aortic root echogram from a patient without aortic root dissection recorded while varying transducer angle so as to sweep the aortic area. The wide dark arrows indicate aortic root width with the beam pointed more inferiorly. The wide light arrows indicate aortic root width with the beam rocked slowly in a superior and medial manner toward the ascending aorta. The thin double-headed arrows indicate aortic wall thickness. Note the variability in aortic root width and aortic wall thickness previously reported as consistent with a localized hematoma.

Table 18

CHEST X-RAY FINDINGS IN AORTIC DISSECTION

1. Superior mediastinal widening
2. Widening of the distal aortic knob
3. A double shadow with calcification visible inside the aortic shadow.
4. A disparity in the sizes of ascending and descending aorta.
5. Cardiomegaly
6. Progressive enlargement of the aorta
7. Deviation of the trachea to the right.

The ultimate definition and extent of dissection has to be established by contrast angiography which will be discussed in detail below. Table No. 19 illustrates the clinical conditions which may closely mimic acute aortic dissection.

Table 19

DIFFERENTIAL DIAGNOSIS OF ACUTE AORTIC DISSECTION

1. Acute myocardial infarction
2. Acute pulmonary embolism
3. Cerebrovascular accident
4. Acute surgical abdomen
5. Rupture of the sinus of Valsalva

INITIAL MANAGEMENT. Based upon the clinical and laboratory features when acute aortic dissection is suspected, immediate measures should be instituted to stabilize the patient's condition before performing any additional studies; intraarterial blood pressure should be closely monitored. If a previous chest x-ray is available for comparison, it would be helpful to see if there has been any enlargement of the mediastinal shadow. Once the diagnosis of acute aortic dissection is apparent, the following steps should be undertaken.

If the patient is hypertensive, blood pressure should be reduced to near normal levels with an agent that causes the blood pressure to come down smoothly rather than drastically. The direct vasodilators which reflexly stimulate the heart should be avoided and, in fact, are contraindicated in acute aortic dissection. When instituting antihypertensive therapy, one should keep in mind that the force and velocity of ventricular contraction (dp/dt) and the pulsatile flow are important determinants of the shearing force acting on the aortic wall. Attempts should be made to decrease the dp/dt with a a suitable agent; drugs that reflexly stimulate the heart such as diazoxide and apresoline should be

avoided. Experimental exposure of the aortas with intimal tears to a nonpulsatile flow at an extremely high blood pressure (440 mm Hg) did not cause dissection, whereas exposure to a pulsatile flow at a considerably lower blood pressure has been shown to cause dissection (48). Figure No. 10 shows a pressure profile of an aorta.

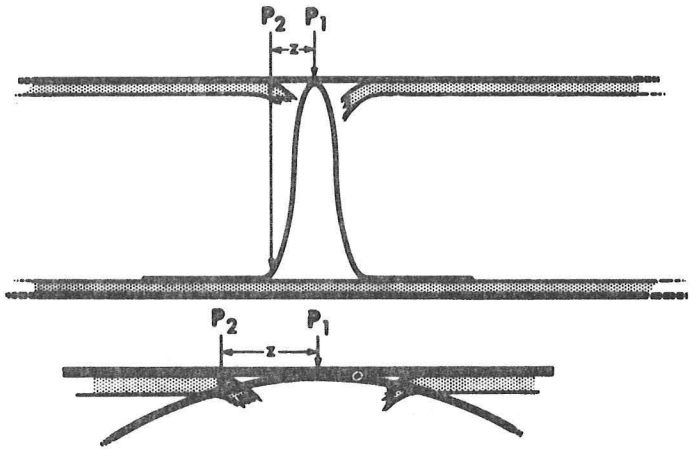


Figure 10: Pressure Profile of Aorta

The concept has been proposed that the driving forces tending to promote the rupture of the aorta are a function of the steepness of pulse wave form. The shape of the curve itself is a function of the compliance of the vessel and the rate of myocardial contractility. The steeper the wave form, the greater will be the pressure differential across the tearing segment Z. The force available to separate the layers and ultimately cause the rupture will be greater if the wave is steeper. Therefore, the object of appropriate antihypertensive therapy is to reduce the velocity of myocardial shortening which can be done with the drugs having negative inotropic effects. Figure 11 shows the temporal relationship between the dp/dt and the rate of dissection (48).

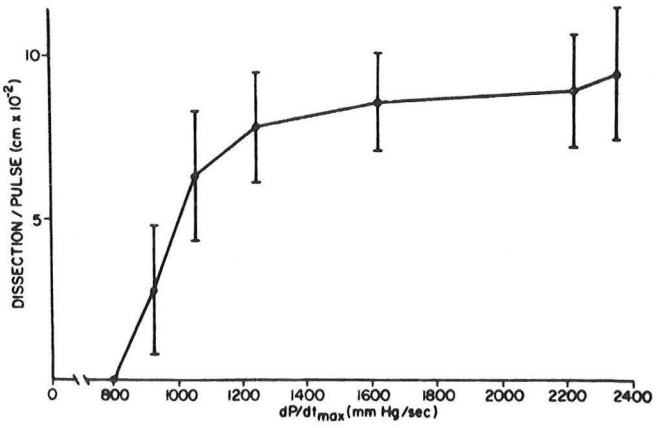


Figure 11: The Relationship Between dp/dt and Dissection

These physical concepts are critical to our understanding of acute aortic dissection and more importantly about the choice of antihypertensive therapy. The blood pressure should be reduced to near normal levels and the ideal agent in this situation would be trimethaphan which has a smooth action and is rapidly effective. Since this drug is a ganglion blocking agent, it decreases the neural transmission at the myocardial contractility sites and has a negative inotropic effect and therefore decreases the pulsatile flow and also blunts the sharpness of the pulse wave generated by the heart. This mode of pharmacological approach in the management has been shown to reduce mortality (49).

The alternative to trimethaphan is sodium nitroprusside in conjunction with the simultaneous administration of a beta adrenergic blocking agent such as propranolol (to reduce the rate of myocardial contractility and arrest the progression of the dissection). Sodium nitroprusside alone has been alleged to cause an increase in dp/dt, an effect that is harmful in these patients (50), the adverse effects of sodium nitroprusside were because of inadequate dosage of propranolol. When adequate doses of propranolol are given along with sodium nitroprusside, this is as effective and indeed is better tolerated than

trimethaphan. The importance of adequate beta blockade along with the infusion of sodium nitroprusside cannot be over-emphasized. Propranolol should be given first as a dose of 0.5 mg intravenously followed by increments of 1 mg every 5 minutes up to a total dose of 0.15 mg/kg or until the clinical evidence of adequate beta blockade as indicated by the heart rate is achieved (51). The clinical application of these drugs are discussed in the second section of this Grand Rounds.

Only after the institution of the immediate measures aimed at restoring the vital signs, should further work-up be undertaken. The goal of initial treatment is the elimination of pain and reduction of systolic blood pressure to 100-120 mm Hg or to the lowest level that is tolerated by the patient with adequate vital organ perfusion.

Angiography. The hazards of this technique are minimal with the proper precautions and most patients tolerate this procedure fairly well if they have been stabilized. Retrograde angiography allows accurate identification of the site of the origin of the dissection, a prerequisite if surgery is to be done. The aortographic findings in acute aortic dissection are shown in the following table.

Table 20

ANGIOGRAPHIC FEATURES OF AORTIC DISSECTION

1. Double channels
2. Entry of dissection
3. Separated intima
4. Reentry
5. Compression of the true aortic lumen by false lumen.
6. Thickening of the aortic wall (normal thickness 2 to 3 mm, in dissection > 5 to 6 mm)
7. Ulcer like projection
8. Extravascular extravasation.
9. Aortic regurgitation
10. Involvement of the aortic branches

In most cases angiography provides conclusive evidence for the diagnosis of acute aortic dissection, but false negatives and false positives are known to occur due to inappropriate projection, layering of the contrast material due to aortic insufficiency or Valsalva effect, clotted aneurysm, neoplasm, etc. Diagnostic errors are unusual in the hands of an experienced radiographer.

DEFINITIVE THERAPY OF ACUTE DISSECTION OF THE AORTA

The choice between continuing medical therapy and surgical intervention depends on the different clinical behavior of proximal and distal dissections in the early phase of the disease. There has been considerable controversy in the literature regarding the surgical vs medical therapy of aortic dissections. With the accumulation of a large number of data, prospective and retrospective in nature, certain generalities can be made. Surgery is the treatment of choice for proximal dissection because of the potentially devastating consequences of the progression of the hematoma and frequent association of this type with pulse deficits, aortic regurgitation, pericardial tamponade and neurological dysfunction etc. In a very small group of patients with proximal dissection (in patients who are unable or unwilling to undergo a surgical procedure), long-term medical therapy has been accomplished with variable results.

For Types 1 and 2, surgery is the treatment of choice. Therefore, the patient with acute Type 1 or 2 dissecting aneurysm who is otherwise a good surgical risk should be taken to the operating room and appropriate corrective surgery should be performed with the adjuvant drug therapy that has been discussed. The superiority of surgical over medical therapy in these types of dissection has been emphasized by several investigators (52-54). The type of surgery for aortic dissection involves definite surgical repair which consists of excision of the intima tear, elimination of the false channel and, when indicated, restoration of the aortic wall competency. From controlled studies (41,55) it appears that surgery is the definitive therapy for patients with Type 1 and Type 2 dissections. The typical analysis of surgical vs medical therapy for different types of aortic dissection from a retrospective study (55) are shown in Tables 21 and 22.

Table 21: Survival of Patients

Survival	No. of Patients According to Type of Dissection			
	Type I	Type II	Type III	Total
Surgically Treated (n = 40)				
Initial	21	5	14	40
At 2 hr	14 (67%)	5 (100%)	13 (93%)	32 (80%)
At 1 wk	11 (52%)	3 (60%)	10 (71%)	24 (60%)
At 1 mo	4 (19%)	3 (60%)	9 (64%)	16 (40%)
At 1 yr	4 (19%)	3 (60%)	7 (50%)	14 (35%)
Medically (Wheat) Treated (n = 12)				
Initial	3	0	9	12
At 2 hr	3 (100%)		9 (100%)	12 (100%)
At 1 wk	1 (33%)		7 (78%)	8 (67%)
At 1 mo	0		3 (33%)	3 (23%)
At 1 yr	0		3 (33%)	3 (23%)
Nonsurgically (excluding Wheat) Treated (n = 22)				
Initial	9	5	8	22
At 2 hr	8 (89%)	3 (60%)	8 (100%)	19 (86%)
At 1 wk	5 (56%)	0	6 (75%)	11 (50%)
At 1 mo	4 (44%)	0	4 (50%)	8 (36%)
At 1 yr	1 (11%)	0	3 (38%)	4 (18%)

Table 22

Comparison of Modes of Therapy, Type of Dissection, and Survival at 1 Year

Treatment	No. of Patients According to Type of Dissection			
	Type I	Type II	Type III	Total
Surgical	4/21 (19%)	3/5 (60%)	7/14 (50%)	14/40 (35%)
Nonsurgical	1/12 (8%)	0/5	6/17 (35%)	7/34 (21%)
Total	5/33 (15%)	3/10 (33%)	13/31 (42%)	21/74 (28%)

For the patients with uncomplicated distal dissection (Type 3), continuation of chronic medical therapy offers a slight, but definite advantage over surgical therapy. The advantage of medical therapy is largely due to the fact that patients with distal dissection tend to have advanced atherosclerotic or cardiac disease. Thus, in these patients, surgical morbidity and mortality are likely to be higher than in patients with proximal dissection even though they are often critically ill. Although chronic medical therapy is recommended for a Type 3 dissection, surgery should be undertaken in these patients if there is evidence of rupture or vital organ compromise or inability to contain the hematoma with appropriate medical therapy.

Summary

Acute aortic dissection is a catastrophic event unless recognized and appropriately treated. All the patients who are suspected to have acute aortic dissections should be stabilized with immediate and appropriate medical therapy, regardless of the ultimate definitive therapy. The immediate reduction in blood pressure should be accomplished by an agent that blunts myocardial contractility and thereby stops the process of dissection. Dissecting aneurysm of the aorta, while potentially fatal, is amenable to aggressive therapy provided one has a strong index of suspicion. Although the management of aortic dissection continues to present a formidable challenge, the prospect of salvaging a majority of patients who survive the first few hours should encourage an aggressive approach.

DISSECTING ANEURYSM

CHOOSE – NITROPRUSSIDE ± PROPRANOLOL
TRIMETHAPHAN
AVOID – DIAZOXIDE
HYDRALAZINE

ACUTE LEFT VENTRICULAR FAILURE

Acute left ventricular failure in a patient with moderate or severe hypertension is an indication for rapid lowering of the blood pressure. The lowering of the blood pressure in a patient with acute pulmonary edema decreases the work load of the failing myocardium and in fact, in many patients, it is possible to restore adequate cardiac function with blood pressure lowering alone. The onset of acute left ventricular failure in the course of severe hypertension reflects the inability of the ventricular pump to sustain the increased work load. The ventricle responds to an increasing systemic resistance by elevating the intraventricular pressure in order to maintain a normal stroke volume at a steady ejection rate. The left ventricular tension in this situation is increased and therefore, the myocardial oxygen demand is also increased. The failing ventricle demonstrates an increased end-diastolic fiber length, an increased ventricular volume and a reduced ejection fraction rate; these factors result in consumption of more oxygen in order to expel a smaller stroke volume. The essential effect that will be required then is an immediate reduction in the systemic vascular resistance in order to decrease the after-load on the failing myocardium and increase the cardiac output. The persistently elevated blood pressure is a costly burden on the failing myocardium increasing its oxygen requirements. This could be particularly deleterious in patients who may have coexistent coronary artery disease. The problem in clinical practice is identifying those cases in which pulmonary edema is secondary to severe hypertension since pulmonary congestion or acute respiratory distress of any kind can reflexly elevate the blood pressure. In these cases, the history and physical examination should assist in coming to a reasonable conclusion. A history of chronic hypertension or hypertensive heart disease, funduscopic evidence of underlying hypertension, a very high diastolic blood pressure (in excess of 120-130 mm Hg) and the failure of the blood pressure to respond rapidly to the administration of oxygen, diuretics and morphine, etc. are evidences for a causal relationship of high blood pressure to pulmonary edema.

Prompt reduction of blood pressure with a vasodilating agent such as sodium nitroprusside is indicated in this situation. Systemic vasodilators such as sodium nitroprusside in addition to their hypotensive effect, dilate the capacitance vessels decreasing the venous return to the heart. These actions therefore decrease the afterload and preload, both of which help to restore myocardial function and increase cardiac output (56). Drugs such as hydralazine and diazoxide should be avoided in treating this condition because they reflexly stimulate myocardial contractility and heart rate. If sodium nitroprusside cannot be infused for any reason and the patient needs parenteral antihypertensive therapy, perhaps small doses of diazoxide can be given.

The other alternative obviously would be trimethaphan which has a smooth onset of action and blood pressure can be predictably lowered by adjusting the speed of infusion. Along with reduction in blood pressure, the conventional measures for managing pulmonary edema should be instituted.

PULMONARY EDEMA

CHOOSE – NITROPRUSSIDE
TRIMETHAPHAN
AVOID – DIAZOXIDE
HYDRALAZINE

SEVERE HYPERTENSION ASSOCIATED WITH ISCHEMIC HEART DISEASE

Systemic hypertension increases the myocardial oxygen consumption by increasing the intraventricular pressure and, in some patients, by increasing the left ventricular diameter, both of which are known to increase the wall tension. Thus, theoretically, patients who have ischemic heart disease and have sustained high blood pressure should benefit from lowering of the blood pressure. Although it is logical to assume that severe hypertension occurring in a patient with ischemic heart disease should be treated, there are no definite data in the literature which uniformly suggest that treatment is beneficial. Despite the reported determintal effects that hypertension may exert on patients with acute myocardial infarction, considerable controversy prevails on the pathophysiological significance of hypertension in patients with acute myocardial infarction. Reduction of blood pressure reduces the cardiac work, wall tension and oxygen demand and is a rational approach to decrease the frequency of angina and limit the necrosis in the early phase of infarction. However, there are conflicting reports in the literature about the value of reducing the blood pressure (to reduce infarct size) in the absence of pulmonary congestion. A relationship between an acute increase in blood pressure and coronary insufficiency has been described (57,58). Although it is believed that hypertension preceeds the onset of chest pain (58), some authors have indicated that hypertension follows rather than precedes the onset of coronary insufficiency. James et al. (59) have demonstrated the presence

of a hypertensive chemoreflex in dogs which is initiated by ischemia in the proximity of the left coronary artery. Whether the hypertension triggers the coronary insufficiency or coronary insufficiency triggers the hypertension, it is likely that extremely elevated blood pressures may impair the function of ischemic myocardium.

Some studies (60,61) suggest that acute elevation of blood pressure in the setting of acute myocardial infarction is transient and does not seem to exert any adverse effect; but Fox et al. (62) have assessed the prognostic significance of acute systolic hypertension in a larger series of patients and have concluded that the mortality rate and the incidence of cardiac failure were significantly greater in a group of patients who had systolic blood pressure greater than 170 mm Hg. The results are summarized in Table 23.

Table 23

ACUTE MI: OUTCOME IN NORMOTENSIVES AND PATIENTS WITH SBP > 170 MM HG (REF 62)

	NO. PTS	AGE	PREVIOUS CAD	MORTALITY	CHF	ARRHYTHMIAS
SYSTOLIC HYPERTENSION	106	58 ± 10	31	13(12%)	35(33%)	22 (21%)
CONTROLS	106	57 ± 10	38	2(2%)	10(9%)	5 (5%)

Shell and Sobel (63) have indicated that reduction of systemic arterial pressure early in the course of acute myocardial infarction protects the myocardium as reflected by reduced release of CPK enzyme activity. In their series, the myocardial infarct size was decreased by 24% in hypertensive patients whose blood pressure was reduced with trimethaphan during the acute phase of myocardial infarction. The results of the study are shown in Figure 12. It is reasonable to assume that hypertension would raise the ventricular afterload and thus, may augment the myocardial oxygen demand and may further compromise the coronary circulation.

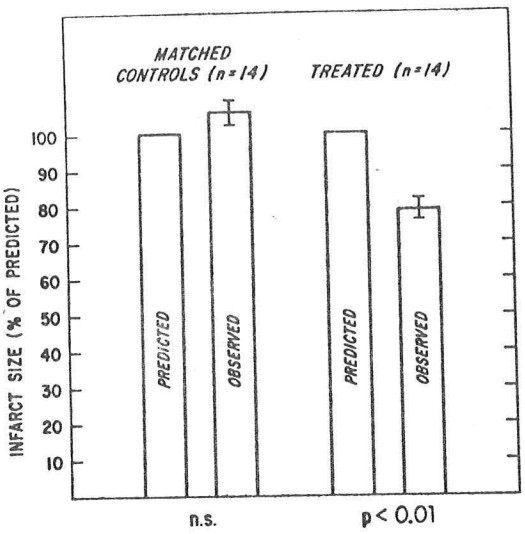


Figure 12: Comparison of values for predicted and observed infart size in normotensive controls and treated patients (Ref. 63)

Cautious treatment of hypertension in patients with acute myocardial infarction is likely to be beneficial. However, the reduction in the blood pressure should be carried on with adequate hemodynamic monitoring. Of the parenteral agents, sodium nitroprusside was widely used in some institutions. On the other hand, in a comparative study utilizing nitroprusside and nitroglycerine for blood pressure reduction in patients with acute myocardial infarction, it was shown that whereas nitroglycerine reduced the electrocardiographic ischemic injury, sodium nitroprusside caused an increase in the magnitude of ST segment elevation (64), (Figure 13). The increase in the heart rate that occurred during nitroprusside infusion could be a factor in the augmented ST segment elevation with this drug. However, the increments in the heart rate were rather moderate. Another possibility is that nitroglycerine has been shown to cause a favorable redistribution of myocardial flow to ischemic areas in contrast to nitroprusside in experimental animals. Diazoxide should be avoided in this situation because of its adverse hemodynamic effects, namely tachycardia and increased myocardial contractility which would further jeopardize the extent of myocardial infarction. It must be emphasized that degree of blood pressure reduction should depend solely on the demonstration of salutary hemodynamic response obtained in a given patient and not to any predetermined level. It should also be emphasized that maneuvers to reduce the blood pressure in acute myocardial infarction should be only undertaken under the guidance of adequate hemodynamic monitoring since the aortic diastolic pressure is a major determinant of coronary blood flow and unwanted reductions in the blood pressure could further compromise the already critical situation.

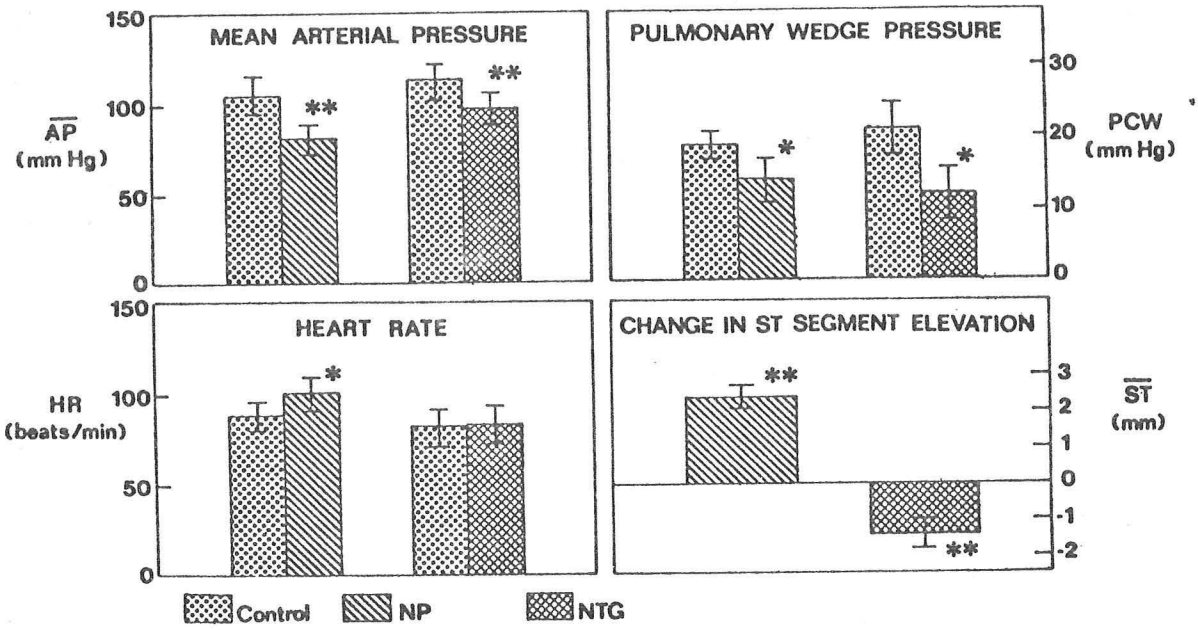


Figure 13: Effects of nitroprusside and nitroglycerin on MAP, heart rate, pulmonary pressure and ST segment elevation. (Ref. 64)

ECLAMPSIA

For practical purposes, eclampsia can be called hypertensive encephalopathy occurring in a pregnant patient. The pathophysiologic mechanisms of eclampsia of pregnancy remain obscure. Eclampsia is characterized by edema, proteinuria, severe hypertension and convulsions. The presenting manifestations of eclampsia do not differ from those of hypertensive encephalopathy except that the dominant feature is convulsions.

The management of eclampsia is directed only partially toward the control of blood pressure elevation which mainly benefits the mother. Successful antihypertensive therapy has not been shown to significantly enhance the fetal survival rate. Magnesium sulfate which is popularly used in this condition is aimed at diminishing neuromuscular excitability. For many years obstetricians have successfully used parenteral hydralazine in this condition. When toxemia of pregnancy presents as a serious hypertensive crisis, potent antihypertensive therapy should be

instituted promptly. The drugs of choice in eclampsia are sodium nitroprusside and diazoxide. With the latter drug, one should keep in mind its inhibitory effect on labor (65), but this effect can be overcome by the administration of oxytocic drugs. Thus, diazoxide is not contraindicated in eclamptic patients as long as one is aware of the possibility of temporary inhibition of labor by this agent. Trimethaphan crosses the placental barrier freely and therefore induces the risk of *meconium ileus* in the fetus. Despite the availability of potent antihypertensive drugs, hydralazine continues to be successfully used in the treatment of eclampsia because it does not reduce myometrial blood flow.

ECLAMPSIA

CHOOSE – NITROPRUSSIDE
HYDRALAZINE
DIAZOXIDE
AVOID – TRIMETHAPHAN
? PROPRANOLOL

PHEOCHROMOCYTOMA CRISIS

The pheochromocytoma crisis is an extremely rare situation requiring emergency control of the blood pressure. It presents with a constellation of striking clinical features. Typically, the blood pressure is markedly elevated to as high as 300 mm Hg systolic, usually with a proportionate rise in the diastolic blood pressure and profound sweating. There is also marked tachycardia, pallor, especially of the face, numbness, tingling and coldness of the feet and hands. Many patients complain of pounding headache, nausea, vomiting and epigastric discomfort. During the crisis, acute pulmonary edema and serious neurological deficits might result. The electrocardiogram reveals various types of tachycardias, but usually of the sinus variety or supraventricular tachycardia. A single attack will last from a few minutes to hours and may occur as often as several times a day to once a month or less. During the intervening periods, however, the patient is usually asymptomatic. Although severe hypertension is a notable finding, this is more so when the tumor is predominantly secreting norepinephrine. Epinephrine producing tumors may not cause marked elevations in the blood pressure.

Once the diagnosis of pheochromocytoma is apparent, an intravenous line should be established and the patient given the alpha adrenergic blocking drug, phentolamine in the dose of 5 to 10 mg intravenously. The dosage of phentolamine may be repeated in a few minutes as warranted by the patient's clinical status. An alternative to phentolamine therapy would be sodium nitroprusside, but the former is more rational. There is no unanimity about the use of the beta blocking drug, propranolol in managing pheochromocytoma crisis. The drug will be certainly useful if the patient has a concomitant cardiac arrhythmia. The administration of beta blocking agents should always be preceded by either phentolamine or phenoxybenzamine. If this is not done, the beta blocker can aggravate the unopposed peripheral vasoconstriction.

CLONIDINE WITHDRAWAL SYNDROME

A syndrome mimicking pheochromocytoma crisis has been reported following abrupt discontinuation of the antihypertensive drug, clonidine (66,67). Clonidine exerts its antihypertensive effect by stimulating the alpha receptors in the brain stem and thus reducing the tone of peripheral sympathetic activity. When the clonidine was abruptly discontinued, or even sometimes rapidly tapered, a specific syndrome has been noted. The patients experience nausea, palpitations, anxiety, sweating, nervousness and headache, all in conjunction with marked elevation of the blood pressure. In some patients, overshoot in blood pressure has been reported following abrupt cessation of clonidine therapy. The possible mechanism of the so-called clonidine withdrawal syndrome is explainable by enhanced sympathetic activity upon sudden discontinuation of drug therapy. The incidence of this peculiar syndrome is very low and in several patients, there appears to be only a rapid return of blood pressure towards the pretreatment level, rather than a rebound in the blood pressure (68). Similar rapid elevations in BP have been rarely reported following abrupt discontinuation of the other centrally acting antihypertensive agents, methyldopa and guanabenz.

Management. When a patient presents with a syndrome of sympathetic overactivity and a history of therapy with clonidine, one should entertain the possibility of clonidine withdrawal syndrome and promptly institute appropriate therapy. The symptoms of clonidine withdrawal can be abated with reinstitution of clonidine alone if this can be done. If there is marked elevation of blood pressure and the patient is experiencing severe and annoying subjective side effects, such as palpitations, chest discomfort, epigastric discomfort, etc., intravenous administration of phentolamine is recommended. The treatment of clonidine withdrawal syndrome does not differ significantly from that of pheochromocytoma. The clonidine withdrawal phenomenon, although extremely rare, can be minimized by precautions to avoid abrupt discontinuation of the drug.

HYPERTENSIVE CRISIS ASSOCIATED WITH DRUG AND FOOD INTERACTIONS MONOAMINE OXIDASE INHIBITORS

Patients receiving monoamine oxidase inhibitors are at a risk of developing hypertensive crisis if they should also take drugs such as ephedrine, amphetamine or foods containing high quantities of tyramine. Monoamine oxidase inhibitors are sometimes used to treat depression and examples of the drugs belonging to this class are listed in the following table.

Table 24

MAO INHIBITORS	FOODS OR SUBSTANCES WITH HIGH TYRAMINE CONTENT
PARGYLINE (EUTONYL)	CHIANTI WINE, SOME BEERS
NIALAMIDE (NIAMID)	AGED CHEESE (CHEDDAR, BRIE)
FURAZULIDONE (FUROXONE)	AVOCADOS, BANANAS, CHOCOLATE
PHENELZINE (NARDIL)	CHICKEN LIVER, FERMENTED SAUSAGE
TRANYLCYPROMINE (PARNATE)	SOY SAUCE, YEAST EXTRACT

Critical elevation of blood pressure has been reported following the interaction between these MAO inhibitors and certain foodstuffs (69,70). The tyramine which is contained in these foodstuffs is an indirectly acting sympathetic amine and is ordinarily destroyed by MAO present in the liver and gastrointestinal mucosa. But in the presence of an inhibitor of MAO, tyramine escapes the oxidative degradation and enters the systemic circulation and potentiates the actions of catecholamines. The ingestion of certain beverages such as Chianti wine, certain foreign beers, foodstuffs including unpasteurized cheeses, pickled herring, chicken livers, yeast, all of which contain significant amounts of tyramine can provoke a hypertensive reaction in patients who are taking MAO inhibitors. The severity of the hypertensive paroxysm so induced is similar to that of pheochromocytoma since both syndromes are mediated by increassed circulating catecholamines. The pressor reaction usually occurs only after several weeks of treatment with MAO inhibitors, but sometimes the duration of the treatment may be as brief as two to three days. Sympathomimetic amines such as those contained in the nonprescription cold remedies are also provocative agents. The hypertensive attack occurs from 1 to 2 hours after eating, having an abrupt onset and may sometimes last up to several hours. The relationship between an MAO inhibitor and the ingestion of a tyramine containing food

is shown in Figure No. 14. Characteristically, the patient feels acutely ill with headache, sweating, palpitations, a sense of impending doom and the blood pressure is often elevated to alarming levels. Pulmonary edema, cardiac arrhythmias, cerebrovascular accidents and acute myocardial infarction have all been noted during these episodes. The diagnosis of a pressor reaction secondary to MAO inhibitors depends upon the history of the usage of the drug and identification of the precipitating event, such as a particular drug or foodstuff. The history of psychiatric depression is often a helpful clue in suggesting the diagnosis.

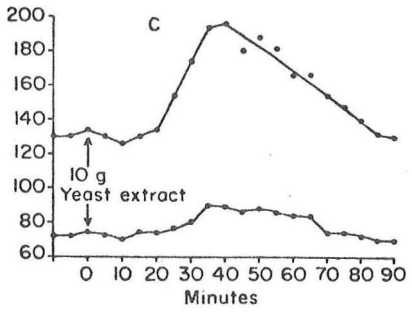


Figure 14: Rise in BP following ingestion of yeast by a patient on MAO inhibitor.

Rapid intravenous injection of 5 to 10 mg of phentolamine will control the hypertension and can be repeated as necessary until the patient is stabilized or switched to an alternative medication such as sodium nitroprusside or infusion of phentolamine. Luckily, these pressor reactions are self-limited and are usually short-lived, but nevertheless, proper recognition of the syndrome is essential in order to institute rational therapy.

HYPERTENSIVE CRISIS - MISCELLANEOUS CAUSES

Hypertensive Crisis in the Postoperative Period. Open heart operations and surgical manipulation of the carotid artery are sometimes followed by severe hypertension in the immediate postoperative period. Hypertension, even if it is of moderate degree, in the postoperative period may jeopardize the integrity of the vascular suture lines. Whatever the etiology for hypertension in the postoperative period may be, it should be managed promptly with parenteral agents. Sodium nitroprusside is usually the agent of choice because of the titratable dose. (Obviously, hypotension should be avoided in the postoperative period because of the danger of thrombosis around the vascular suture lines.) Trimethaphan should be avoided in the postoperative period because it may delay the return of bowel and bladder function.

Severe hypertension associated with body burns. The hypertension crisis associated with extensive body burns is an uncommon occurrence and the mechanism involved is not understood. The blood pressure may rise to critical levels and require the use of a promptly acting agent as sodium nitroprusside or diazoxide.

Hypertensive Crises in Quadriplegic Patients. Hypertensive crises have been reported in patients with high transverse lesions of the spinal cord, usually above the origins of the thoraco-lumbar sympathetic neurons (71,72). The mechanism appears to be one of autonomic over-activity. The subjects with lesions at T5 level or above have attacks of autonomic hyperreflexia. Any stimulation of dermatomes and muscles supplied by nerves below the injury evokes severe hypertension, profound headache and bradycardia. The hypertension may be often quite severe and may indeed cause cerebrovascular accidents and death. This so-called autonomic hyperreflexia occurring in quadriplegics has been mistakenly diagnosed as pheochromocytoma and toxemia of pregnancy (71). The blood pressure crisis is the result of excessive stimulation of sympathetic neurons and the associated bradycardia is probably due to the excitation of the baroreceptor reflexes. Given the current patho-physiological basis for such hypertensive reactions, these critical blood pressure elevations can be prevented by avoiding the excessive stimulation of the susceptible portion of dermatomes. The hypertension should be treated with one of the parenteral antihypertensive drugs discussed.

TREATMENT OF HYPERTENSIVE EMERGENCIES

The availability of potent antihypertensive drugs within the last few years has revolutionized the therapeutic approach to hypertensive crises. The drugs which can be administered parenterally to reduce the blood pressure are shown in the following table.

Table 25

DRUGS FOR THE TREATMENT
OF SEVERE HYPERTENSION

NITROPRUSSIDE

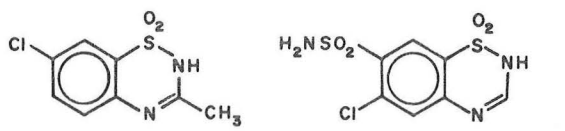
DIAZOXIDE

TRIMETHAPHAN

HYDRALAZINE

An important consideration in treating patients with hypertensive emergencies is the rapidity of onset and duration of action of the drug given. The other consideration should be the knowledge of possible hemodynamic effects of the drug on the patient. The patient's clinical, neurological and hemodynamic status should be assessed before beginning antihypertensive therapy. The choice of the antihypertensive agent depends largely on the hemodynamic status of the patient.

Diazoxide. Diazoxide is a benzothiadiazine derivative which closely resembles the thiazide diuretics (Figure No. 15), but, it is quite different pharmacologically. When given intravenously, it has a direct relaxant effect on the vascular smooth muscle causing a rapid fall in arterial blood pressure. The hypotensive effect of diazoxide is associated with striking increases in heart rate and cardiac output.



DIAZOXIDE CHLOROTHIAZIDE

Figure 15: Structures of diazoxide and chlorothiazide.

Mechanism of action. Diazoxide exerts its hypotensive action entirely by reducing the peripheral vascular resistance by direct relaxation of the smooth muscle (73,74). Diazoxide has no effect on the capacitance vessels and therefore, the venous return to the heart is not impaired. This contributes to the increased cardiac output, which, in turn, partly counteracts the hypotensive effect of diazoxide.

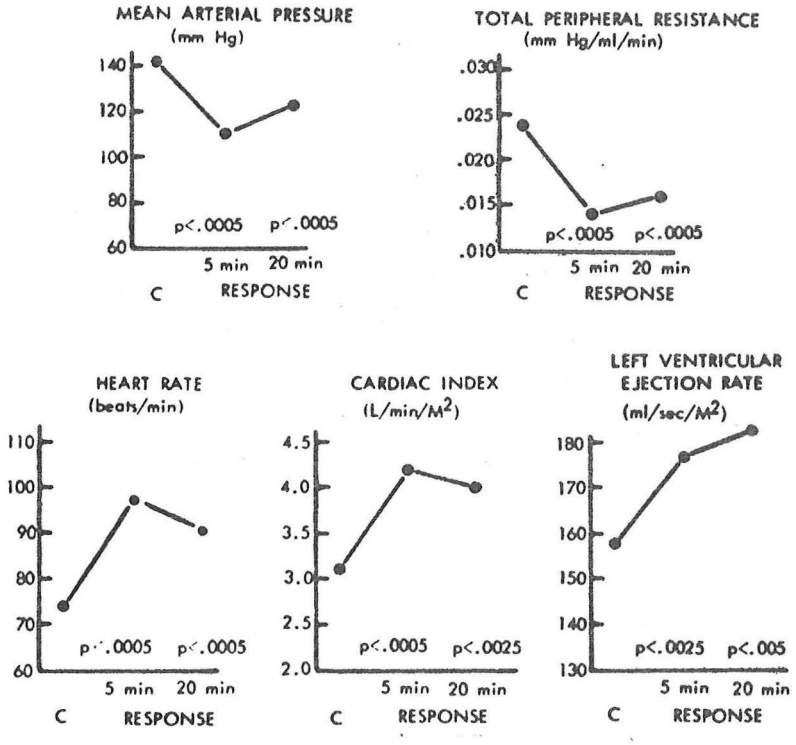


Figure 16: Hemodynamics of diazoxide (Ref. 97)

Diazoxide has no direct effect on the myocardium, but the reflex increases in the cardiac output and heart rate might be poorly tolerated by patients with intrinsic cardiac disease. This effect is an important consideration in the choice of therapy for patients with cardiac disease. The blood flow to all vascular beds, including the renal and cerebral, is usually maintained. Since diazoxide does not inhibit the autonomic reflexes, postural hypotension is not a problem. Expansion of plasma volume and edema formation occur during diazoxide therapy (75,76) and these effects seem to be more marked than is usual with other antihypertensive drugs, because of its direct tubular antinatrietic action (77).

Clinical use. Intravenous administration of diazoxide produces a rapid fall in blood pressure within one minute and the maximum effect is achieved within two to five minutes, as shown in Figure 17 (74,78).

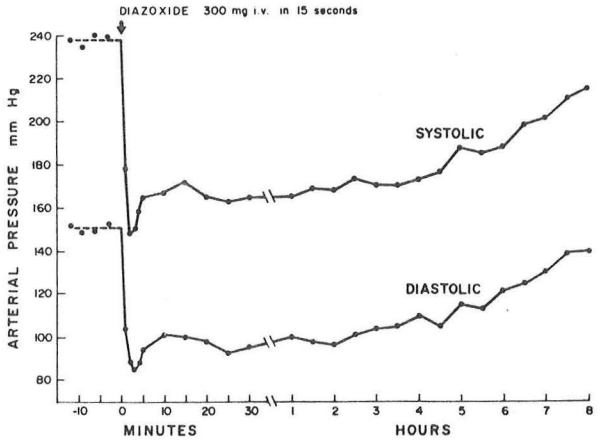


Figure 17: Usual response to 300 mg diazoxide.

The hypotensive effect of a single injection of diazoxide is maintained for 3 to 15 hours, but if there is no effect from the first injection, an additional dose can be given within 30 minutes. Traditionally, the recommended dose of diazoxide is 300 mg or 5 mg/kg/wt given as a rapid intravenous injection. To be maximally effective, the dose should be injected rapidly, between 10 to 30 seconds. This rapid injection is necessary to overcome the protein-binding effect of diazoxide (79). The injection should always be made into a stable intravenous line; since diazoxide is highly alkaline (pH 11.6), extravasation can cause severe local pain and cellulitis. Thus, every precaution should be taken to prevent the leakage of diazoxide. Some recent studies (80,81) indicate that diazoxide can be given by slow intravenous infusion, but further studies are needed before concluding that diazoxide infusions are effective. Several reports (76,82,83) have attested to the usefulness of the standard dose of diazoxide (300 mg) in the treatment of severe hypertension. However, injection of this relatively large single dose makes no allowance for variation in response and commits the physician to whatever degree of hypotensive effect that may ensue. Severe hypotension (84,86) with resultant myocardial ischemia (85,87,88) and cerebral vascular insufficiency (85,88) have been reported with the standard 300 mg dose of diazoxide. To date, at least 40 major morbid events have been reported after a standard dose of diazoxide injection, including five deaths, two strokes and four myocardial infarctions (88).

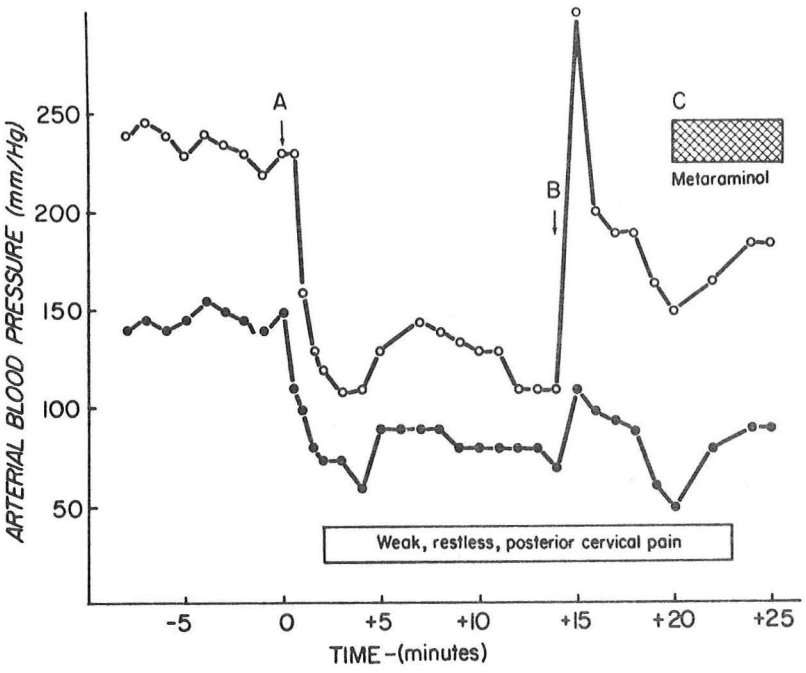


Figure 18: Unusual response to 300 mg diazoxide injection.

We have evaluated the effectiveness of smaller dose bolus injections of diazoxide for the treatment of severe hypertension (89), reasoning that "mini-bolus" injections of diazoxide, if effective, would reduce the dangers of drastic and precipitous reduction in blood pressure. The results of our study done at the Parkland Hospital are shown in Figures 19 and 20 and Table 26.

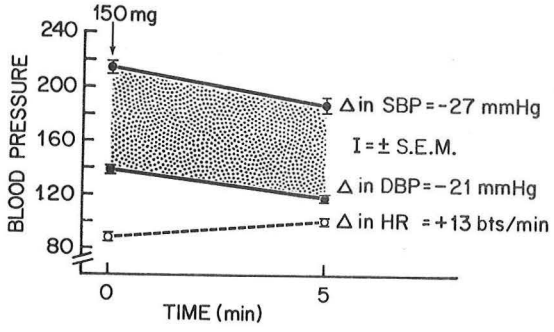


Figure 19: BP response to "mini" bolus (150 mg) of diazoxide (Ref. 89)

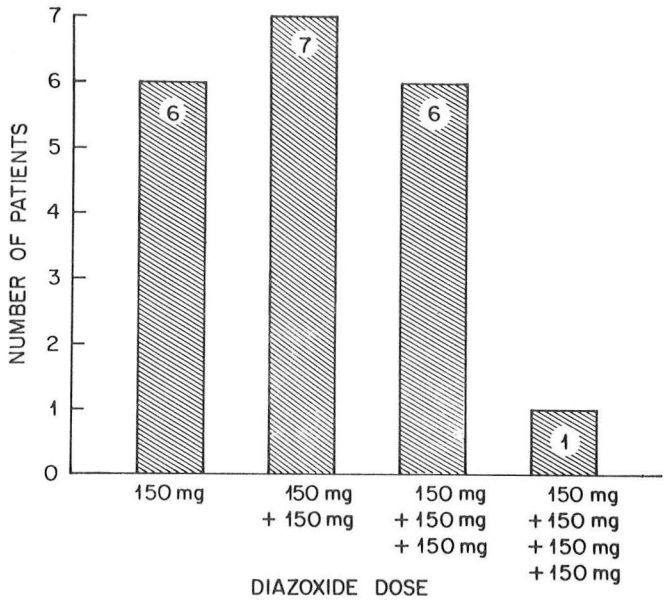


Figure 20: Total dose of diazoxide required to lower DBP < 110 in 20 patients. (Ref. 89)

Table 26

Comparison of Patients Requiring One or More Than One Injection of 150 mg of Diazoxide

	One Injection (6 patients)	More Than One Injection (14 patients)
Age (yr)	45.3 ± 8.2	46.5 ± 3.3
Body weight (kg)	64.7 ± 4.4	85.1 ± 4.8
Creatinine (mg/dl)	1.18 ± 0.22	1.39 ± 0.22
Baseline blood pressure (mm Hg)		
Systolic	208 ± 10	216 ± 5
Diastolic	132 ± 4.4	141 ± 3
Recent antihypertensive therapy	3 patients: hydrochlorothiazide (1); methyldopa (2)	1 patient: hydrochlorothiazide, propranolol and hydralazine
Funduscopic changes*		
Grade 0–1	3 patients	8 patients
Grade 2	2 patients	2 patients
Grade 3	1 patient	3 patients
Grade 4	None	1 patient

*Keith-Wagener-Barker classification.

In this study, 32 patients with a diastolic blood pressure greater than 125 mm Hg were treated with smaller bolus injections, 105 or 150 mg, which were repeated every five minutes as needed to reduce the diastolic blood pressure to 110 mm Hg or less. As seen in Figure 19, the single injection of 150 mg of diazoxide reduced the systolic blood pressure by 27 mm Hg and diastolic blood pressure by 21 mm Hg. To determine why some patients require more doses of diazoxide than others, we analyzed factors including age, body weight, initial blood pressure, plasma creatinine and recent antihypertensive therapy as shown in Table 26. There were no significant differences in ages and plasma creatinine values of patients who received only one dose or more than one dose of diazoxide. Although the difference in baseline blood pressures was only of borderline significance, patients who required multiple injections of diazoxide had significantly greater body weight ($P < 0.013$). Their relatively greater body weight may explain the need for additional injections. In this study no patient became hypotensive and the drop in blood pressure was not precipitous. One patient remained without complications for the initial 24 hours after diazoxide, but then had a transient hemiparesis. Diazoxide had decreased her blood pressure from 250/145 mm Hg to 190/96 mm Hg. At the time of onset of hemiparesis, her blood pressure was 130/90 mm Hg. Her neurological changes subsequently cleared completely. On the basis of these findings, it is suggested that mini-bolus injections of diazoxide, i.e., 150 mg given every five minutes can be effective in rapidly controlling severe hypertension while providing the advantage of ease of administration and relative freedom from side effects.

Disadvantages of diazoxide. The most common side effects reported with diazoxide include nausea, vomiting, abdominal discomfort, sodium and water retention and a sensation of warmth along the vein. More severe pain is noted when extravasation occurs. The other major side effect is an exaggerated hypotensive effect. The various side effects of diazoxide are listed in the following Table.

Table 27A

POTENTIAL RISKS OF STANDARD DOSE (300 mg) INJECTION OF DIAZOXIDE

1. Excessive response ⟶ Hypotension
2. Sequelae of hypotension ⟶ cerebral, coronary and renal insufficiency
3. Tachycardia

Table 27B

ADVERSE EFFECTS

1. HYPERGLYCEMIA
2. HYPERURICEMIA
3. RETENTION OF SODIUM
4. ↑ FATTY ACIDS
5. HIRSUTISM (PROLONGED ORAL THERAPY)
6. ARREST OF LABOR

The excessive hypotensive effect of diazoxide is particularly likely in patients who have had prior antihypertensive therapy, such as hydralazine, guanethidine or potent diuretics. To counteract the fluid retention, it is a common practice to give 40 or 80 mg of furosemide intravenously. The hyperglycemia due to diazoxide is due to its direct effect on the pancreatic beta cells to reduce insulin secretion (90). The hyperglycemic effect of diazoxide rarely needs a specific therapy. But, blood glucose levels should be monitored, particularly in patients with impaired carbohydrate metabolism and with repeated injections of diazoxide. Failure to follow these precautions has been responsible for the development of diabetic ketoacidosis (91). The hyperglycemia with diazoxide therapy responds to the usual management with insulin. Diabetes mellitus is not a contraindication for the use of diazoxide as long as one takes the appropriate precautions to monitor the blood glucose and tailor the dose of insulin accordingly.

Diazoxide displaces the coumarin anticoagulants from serum proteins (92), and this potentially induces a risk of bleeding in susceptible patients. However, the simultaneous usage of diazoxide and coumadin is unusual and this interaction is not of practical significance. Although hyperuricemia is sometimes seen after administration of diazoxide, this effect is not of importance in most patients because of the limited duration of treatment with diazoxide. Diazoxide is a powerful relaxant of uterine smooth muscle and may arrest labor when used in hypertensive crisis of eclampsia (65), but this inhibitory effect on the uterus can be easily reversed with oxytocin. The other important side effects of diazoxide include tachycardia and palpitations which can be successfully controlled by simultaneous administration of a beta-adrenergic blocking agent such as propranolol.

Table 28

ROLE OF DIAZOXIDE

1. Accelerated or malignant hypertension
2. Hypertensive encephalopathy
3. Eclampsia (caution, inhibitory effect on labor)

Absolute contraindications

a. Patients with acute myocardial infarction
b. Acute dissection of the aorta

NITROPRUSSIDE

Sodium nitroprusside is one of the most potent blood pressure lowering drugs and possesses the distinct property of rapid onset and offset of action. The fears of cyanide intoxication and the time consuming process that was necessary to prepare this drug delayed its acceptance for clinical use. The structure of nitroprusside is shown in Figure 21.

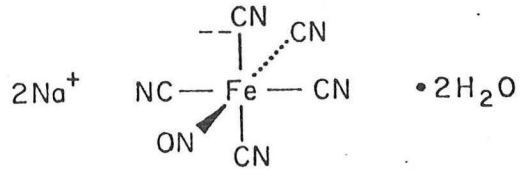


Figure 21: Structure of nitroprusside.

Sodium nitroprusside was synthesized in 1849 (93), but the pharmacological and the toxicological properties of this important drug were not analyzed until 1929 by Dr. Johnson (94). Subsequently nitroprusside fell into oblivion once again and it took another 25 years or so until Page and his associates (95) reported the usefulness of this agent in the treatment of hypertensive crisis. Although the effectiveness of nitroprusside as a powerful blood pressure lowering agent has been clearly demonstrated, it was only in 1974 that this drug was released by the FDA for general use.

The hypotensive response occurs within seconds after infusion is started and is dissipated almost as rapidly when the infusion is discontinued (Figure 22).

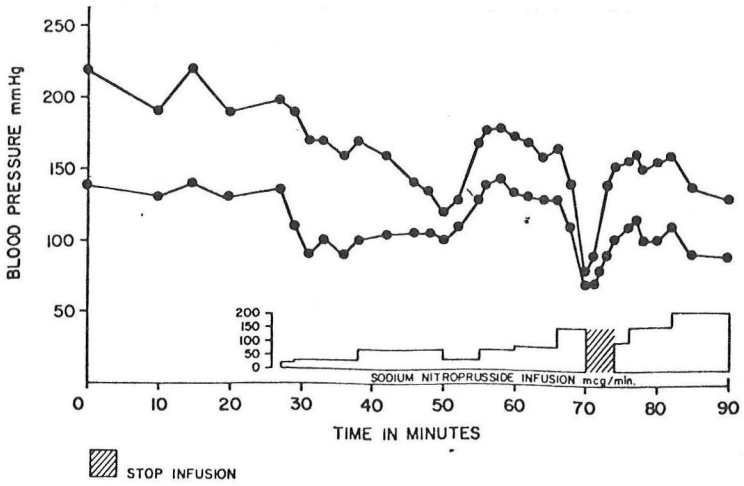


Figure 22: BP response to nitroprusside infusion.

The actions of nitroprusside are almost exclusively confined to the vascular smooth muscle, where it relaxes both the arteries and the veins. During nitroprusside administration, systemic arterial and venous pressures are reduced along with the systemic and pulmonary vascular resistances. Although the exact mechanism by which nitroprusside dilates the vasculature has not been firmly established, it may interfere with the intracellular activation of calcium, thereby inhibiting the release of calcium from storage sites, or by facilitating the extrusion of intracellular calcium or by enhanced sequestration of intracellular calcium. When nitroprusside is infused, heart rate tends to go up only modestly in normal subjects, with greater increases in hypertensive patients (97). The hemodynamic effects of nitroprusside are shown in Figure 23.

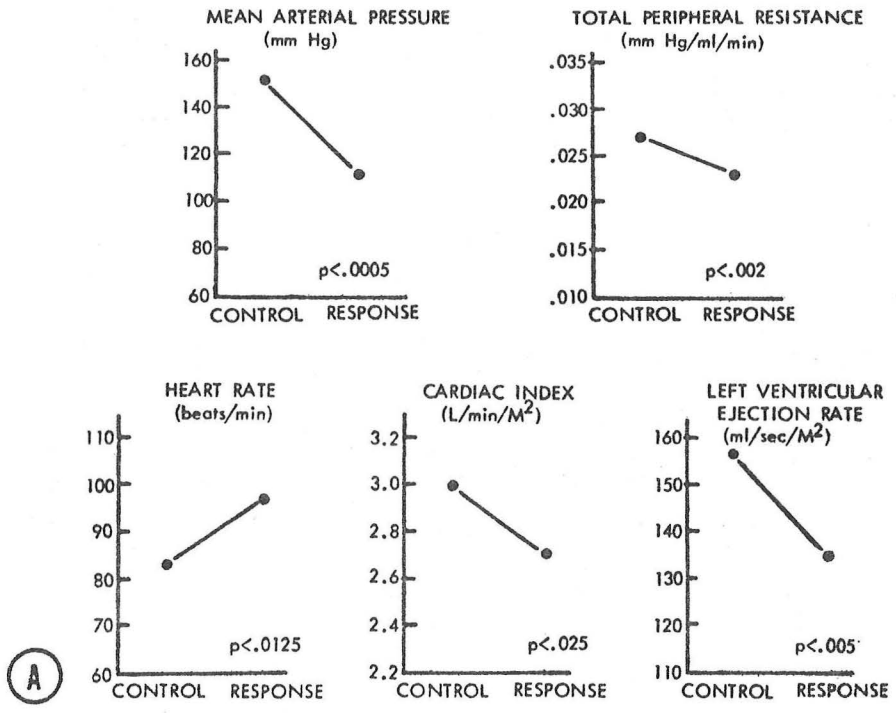


Figure 23: Hemodynamics of nitroprusside

Although there is an increment in heart rate with nitroprusside in normal subjects and those with hypertension, this is not seen in patients with congestive heart failure (98). This observation is important; patients with ischemic heart disease may be given nitroprusside without inducing tachycardia. The cardiac output response is

quite variable and depends largely on the preexisting hemodynamic status of the patient. In hypertensive patients not in congestive heart failure, cardiac output usually falls and in patients with low output states due to cardiac dysfunction, it consistently increases (97,98).

Metabolism. The immediate metabolic product of nitroprusside is cyanide which is probably liberated by the direct combination of nitroprusside with the sulfhydryl groups in the red cells and the tissues. The circulating cyanide is rapidly converted in the liver to thiocyanate (by the enzyme "rhodanase" or "transsulfarase"), which is removed almost exclusively by the kidney with a half-life of approximately one week (95,99).

Method of administration. Sodium nitroprusside is supplied in 50 mg vials of dry powder and is usually reconstituted with 2 to 5 cc of 5% dextrose in water which yields an amber colored solution. The 50 mg thus reconstituted are then added to 500 or 1000 cc of dextrose in water. A more concentrated solution can be made by adding 50 mg of nitroprusside to only 250 cc of dextrose and water for patients in whom fluid restriction is necessary. No diluent other than dextrose and water should be used and no other drugs should be added to the nitroprusside solution. Since nitroprusside is light sensitive, the solution may acquire a darker tint if exposed to light. Because of its rapid onset of action and potency, nitroprusside infusion must be closely and accurately monitored and whenever possible, this should be done by means of an infusion pump or a micro-drop regulator. It is also strongly suggested that intraarterial blood pressure be monitored during nitroprusside infusion to safeguard the patient. To ensure maximal benefit from nitroprusside, the drug should be titrated to effective doses as quickly as possible, but with due caution. Perhaps a safe initial dose is 0.5 µg/kg/min and this can be increased every five minutes until the desired blood pressure level is obtained. It has been said that almost every patient will respond to nitroprusside if a high enough dose is given (96). Once the desired effect of nitroprusside is achieved, the infusion usually can be maintained with minimal adjustment, but the blood pressure should be continuously monitored. The infusions for the treatment of hypertensive crisis are generally for about 12 to 48 hours and should be discontinued as soon as alternate modes of therapy are applied. When stopping nitroprusside infusion, there is no need to wean the patient from the drug gradually. Because of its short duration of action, effects of stopping the therapy will be seen within a few minutes and if indicated, treatment can be reinstituted promptly.

Advantages. The major advantages of sodium nitroprusside are 1) rapid onset of action, 2) potency, 3) short duration of action, 4) smooth regulation of blood pressure.

Adverse Effects. The potential adverse effects are listed in Table No. 29. Hypotension, which is the most common effect of nitroprusside therapy is a consequence of inadequate regulation of the infusion rate. Accidental acceleration of intravenous infusion, faulty infusion equipment or failure to monitor the patient's blood pressure are the usual causes of hypotension.

Table 29

ADVERSE EFFECTS OF NITROPRUSSIDE

HYPOTENSION*

THIOCYANATE TOXICITY

CYANIDE TOXICITY

Thiocyanate Toxicity. The thiocyanate toxicity secondary to nitroprusside is uncommon and occurs only with high doses and in the presence of renal failure. Symptoms of thiocyanate toxicity include fatigue, nausea, anorexia, skin rashes, headaches, disorientation and psychotic behavior. They tend to occur at plasma levels of 5 to 10 mg/dl and death due to thiocyanate toxicity may occur if the plasma levels are greater than 20 mg/dl (96). Therefore, during high dose infusions of nitroprusside and especially when renal function is impaired, periodic determinations of plasma thiocyanate levels are recommended and treatment should be interrupted when the thiocyanate level is close to 10 mg/dl (100). However, most clinical situations demand only short term therapy with nitroprusside; monitoring of plasma thiocyanate levels is not necessary as long as the patient's clinical status is closely assessed. The treatment of thiocyanate toxicity demands discontinuation of the drug and institution of dialysis. Thiocyanate can inhibit thyroidal iodine uptake and has been rarely reported to cause hypothyroidism (101), but in this reported instance, the patient received nitroprusside for nearly 21 days and the hypothyroidism and thiocyanate toxicity were reversed with the institution of dialysis.

Cyanide Toxicity. Cyanide poisoning, feared by chemists for a long time when studying the actions of sodium nitroprusside, has indeed occurred in some patients (102, 103). Nitroprusside is decomposed to cyanide in the blood which is converted rapidly to thiocyanate. The conversion of cyanide to thiocyanate is catalyzed by the enzyme rhodanase in the liver which facilitates the transfer of sulphur to the cyanide molecule in the presence of a sulphur donor (104). Prevention of cyanide toxicity, therefore, is thus dependent on the availability of sulphur and the transsulferase enzyme. This enzyme may be deficient in such extremely rare conditions as Leber's atrophy or tobacco amblyopia (105).

High levels of plasma cyanide concentration have been noted following infusion of nitroprusside at high rates (106), but the blood cyanide levels are not helpful in predicting toxicity since these levels do not necessarily correlate with the tissue cyanide concentration. The cyanide combines with the cytochrome C of the respiratory chain and produces inhibition of aerobic metabolism. The prevention or treatment of cyanide intoxication should be directed towards decreasing the cyanide binding to cytochrome C and to remove the cyanide from the blood. Thiosulfate infusion may exert a favorable effort by acting as a sulphur donor thereby facilitating the conversion of cyanide to thiocynate.

Recently, Cottrell and colleagues (107) have demonstrated that prophylactic infusion of hydroxycobalamin, (Vit B_{12a}) 25 mg per hour, decreased the RBC cyanide concentration and tissue hypoxia resulting from nitroprusside infusion during surgery (Figures 24 and 25).

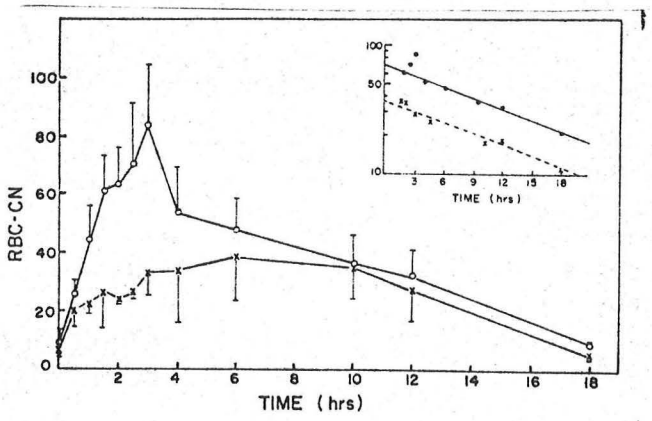


Figure 24: Red-Cell Cyanide (in Micrograms per 100 ml) after Nitroprusside (SNP) Alone (Upper Curve, Open Circles) and after Nitroprusside and Hydroxocobalamin (B_{12a}) (Lower Curve).
The upper right hand corner shows the semilog plot of red-cell cyanide (upper curve) and plasma cyanide times 10 (lower curve) in the absence of B_{12a}. (Ref. 107)

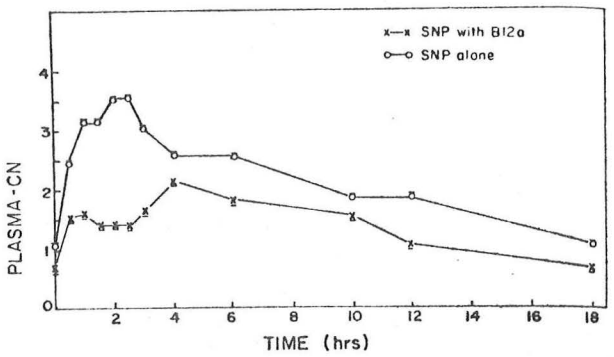


Figure 25: Plasma Cyanide (in Micrograms per per 100 Ml) after Nitroprusside Alone (Upper Curve) and after Nitroprusside and Hydroxocobalamin (Lower Curve). (Ref. 107)

Hydroxycobalamin has one cyanide radical less than the cyanocobalamin, and therefore allows cyanide to combine and form cyanocobalamin which is then excreted in the urine. Toxicity from the doses of hydroxycobalamin used, have not been described. Therefore infusion of hydroxycobalamin, separately or with nitroprusside represents a significant advance in our management of the toxicology of sodium nitroprusside and can be used for suspected cyanide intoxication if simply stopping the nitroprusside fails to correct the toxicity.

Resistance and tachyphylaxis to sodium nitroprusside has been reported only very rarely and the high doses of nitroprusside required in these rare instances have caused fatalities (102,103). The resistance was characterized by greater than normal requirements for nitroprusside, metabolic acidosis and an increase in the mixed venous oxygen tension. This phenomenon of resistance is not well understood, but the unusually great requirements for nitroprusside lead to speculation as to whether the metabolic products of nitroprusside influence the actions of nitroprusside on the vascular muscle. In a recent study (108), dose response curves for norepinephrine were obtained in the isolated rabbit aortic strips; sodium nitroprusside alone shifted the dose response curve to the right, i.e., the nitroprusside inhibited the actions of norepinephrine significantly. However, the shift was less when the aortic strips were exposed to both sodium nitroprusside and sodium cyanide (Figure 26). When the cyanide alone was added to the aortic strips, the response to norepinephrine was unchanged. These results indicate that cyanide itself antagonized the actions of sodium nitroprusside *in vitro* and explain the rare instances of tachyphylaxis to nitroprusside therapy.

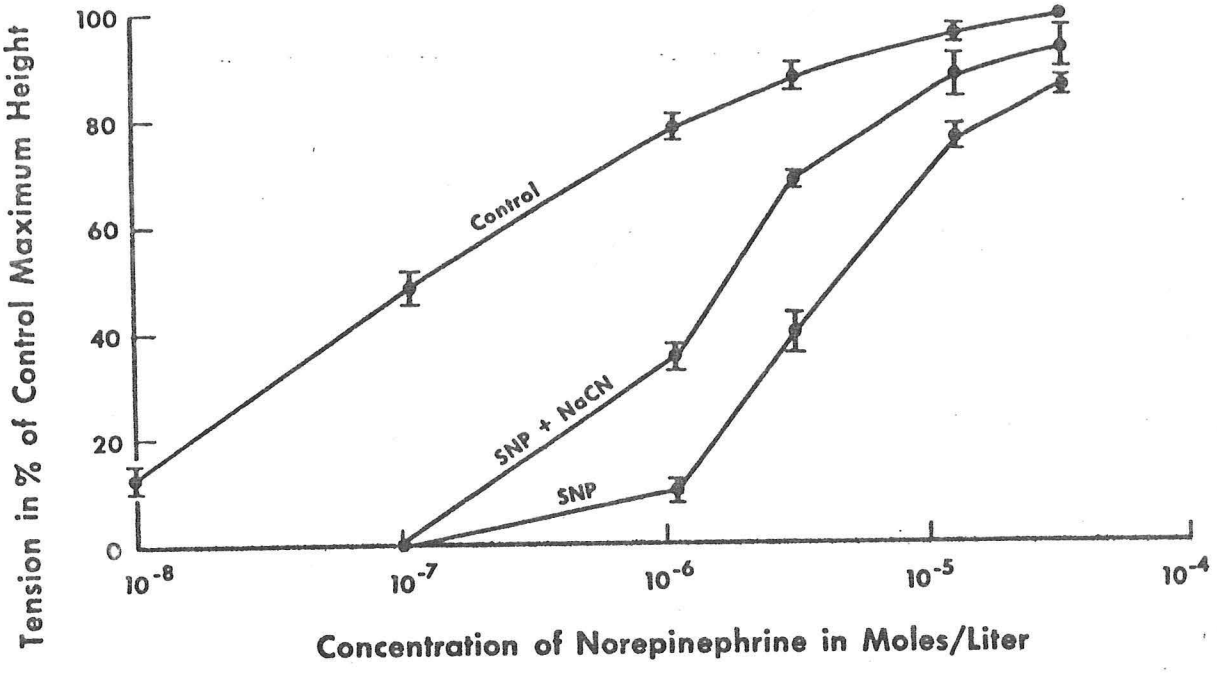


Figure 26: Dose-response curves obtained for rabbit aortic strips with various concentrations of norepinephrine in mol/l. Tension is expressed as percentage of the control maximum height. SNP (10^{-5} m) was added 2 to 5 min before norepinephrine challenge. SNP (10^{-5} m) and sodium cyanide (10^{-4} m) were added 2 to 5 min before norepinephrine challenge. A significant shift of the dose-response curve to the right occurred with SNP alone, but a significant shift to the left occurred with SNP and sodium cyanide ($P < .05$). (Ref. 108)

Other side effects. Sodium nitroprusside has caused mild thrombocytopenia (110) and methhemoglobinemia (109), but the clinical importance of these adverse effects is not known because of their rarity. Experimentally, nitroprusside has been shown to inhibit hypoxia-mediated vasoconstriction in the pulmonary vasculature and therefore may increase perfusion of nonventilated areas of lung (111). This effect is probably of no consequence generally, but could be harmful for subjects with large nonventilated areas of the lung or in whom severe hypoxemia is already present.

TRIMETHAPHAN (ARFONAD)

Trimethaphan Camsylate is a ganglion blocking agent useful in the emergency treatment of hypertension. Trimethaphan competitively inhibits the action of acetylcholine in the post-ganglionic nerve terminals and prevents post-synaptic depolarization by stabilizing the membrane (112). This agent has no effect on post-ganglionic catecholamine release, nor does it have any direct action on the vascular smooth muscle. The hypotensive effect of trimethaphan is accompanied by a reduction in the cardiac index, left ventricular ejection rate and cardiac output (97,113), (Figure 27).

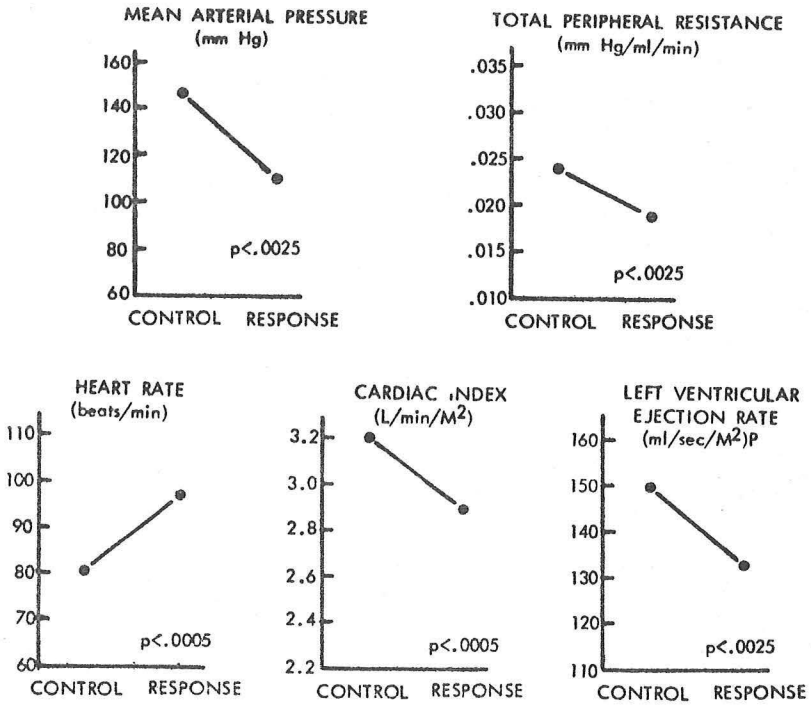


Figure 27: Hemodynamic effects of trimethaphan

A rise in cardiac output may be seen in hypertensive patients with congestive heart failure, reflecting a reduction in the venous return induced by this drug, a property it shares with sodium nitroprusside. Sometimes an insignificant reflex increase in the heart rate results from incomplete autonomic blockade. Trimethaphan has a rapid onset of

action and the effects dissipate within a few minutes of discontinuation of the drug. The effect on blood pressure is primarily an orthostatic one so that substantial doses are necessary to reduce the blood pressure in supine patients. The head end of the bed should be elevated to augment the antihypertensive effect of this agent. Trimethaphan should be administered as a continuous intravenous drip, similar to sodium nitroprusside, and constant monitoring is necessary, preferably in the intensive care unit. For infusion purposes, 500 mg of trimethaphan should be mixed in 500 ml of dextrose in water which gives a concentration of 1 mg/ml. The usual starting dose of the drug should be about 1 mg/min and titrated to obtain the desired blood pressure level. The hypotensive effect is immediate and returns to pretreatment levels once the infusion is stopped. Prolonged infusion of trimethaphan causes tachyphylaxis due to intravascular volume expansion, which can be partially overcome by effective diuretics.

Table 30

ADVANTAGES OF TRIMETHAPHAN

1. Rapid onset and offset of action
2. Smooth blood pressure control can be maintained with careful titration of the dose.
3. Brief duration of action
4. Favorable effects on the myocardium, namely, decrease in cardiac index and left ventricular ejection rate. This effect makes it an agent of choice in acute aortic dissection where the reduction in the rate of myocardial contractility and left ventricular wall tension are desirable in order to arrest the progression of the dissection.

Disadvantages. The major disadvantage of trimethaphan is that it causes parasympathetic inhibition that leads to paralytic ileus, urinary retention and mydriasis. These effects are particularly likely to occur when the drug is administered for more than 24 hours. An indwelling urinary catheter may be necessary when trimethaphan is given for more than two or three days. Inactivation of pupillary reflexes by trimethaphan may make it difficult to evaluate the neurological status of patients with hypertensive encephalopathy or intracranial hemorrhage. The bowel paralysis induced by this agent may delay the post-operative recovery period. Trimethaphan should be used with caution in allergic individuals because of its potential to liberate histamine (114). It is also recommended that patient's respiratory status be monitored closely particularly if large doses of trimethaphan are used because of the remote possibility of respiratory depression by this drug (115).

Table 31: Hemodynamic Effects of Sodium Nitroprusside, Trimethaphan and Diazoxide

	Sodium nitroprusside	Trimethaphan	Diazoxide
Mean arterial blood pressure	↓	↓	↓
Heart rate	↑	↑	↑
Cardiac index	↓	↓	↑
Total peripheral resistance	↓	↓	↓
Left ventricular ejection rate	↓	↓	↑

PHENTOLAMINE

Phentolamine, an alpha receptor blocking agent, is specifically indicated for treating hypertensive crises associated with increased circulating catecholamines, namely pheochromocytoma crisis, certain cases of clonidine withdrawal syndrome and crises resulting from MAO inhibitor and drug-food interaction. This drug is not effective in treating hypertensive crises from other causes. The hypotensive effect of a single intravenous bolus injection is short-lived and lasts less than fifteen minutes. It is perhaps preferable to use sodium nitroprusside infusion instead of phentolamine infusion because the former drug is effective in treating any type of severe hypertension and is somewhat easier to handle than phentolamine.

RECENT ADVANCES IN THE TREATMENT OF HYPERTENSIVE EMERGENCIES

1. Angiotensin converting enzyme inhibitor (SQ 20881). Angiotensin converting enzyme is responsible for converting angiotensin I to angiotensin II which is the most powerful vasoconstrictor. Angiotensin II has been incriminated in sustaining certain forms of hypertension. Recently some workers (116) have successfully employed the inhibitor of angiotensin converting enzyme, teprotide (SQ 20881) in the treatment of hypertensive emergencies. The patients who responded to the injection of SQ 20881 (Figure 28) were thought to have renin dependent hypertension whereas the patients who did not respond to this drug were considered to be volume dependent and therefore were treated successfully with diuretic agents. Although these results are preliminary and

need to be confirmed in a larger series of patients, understanding of the pathophysiology of certain forms of severe hypertension may dictate a specific role for this drug in certain hypertensive emergencies.

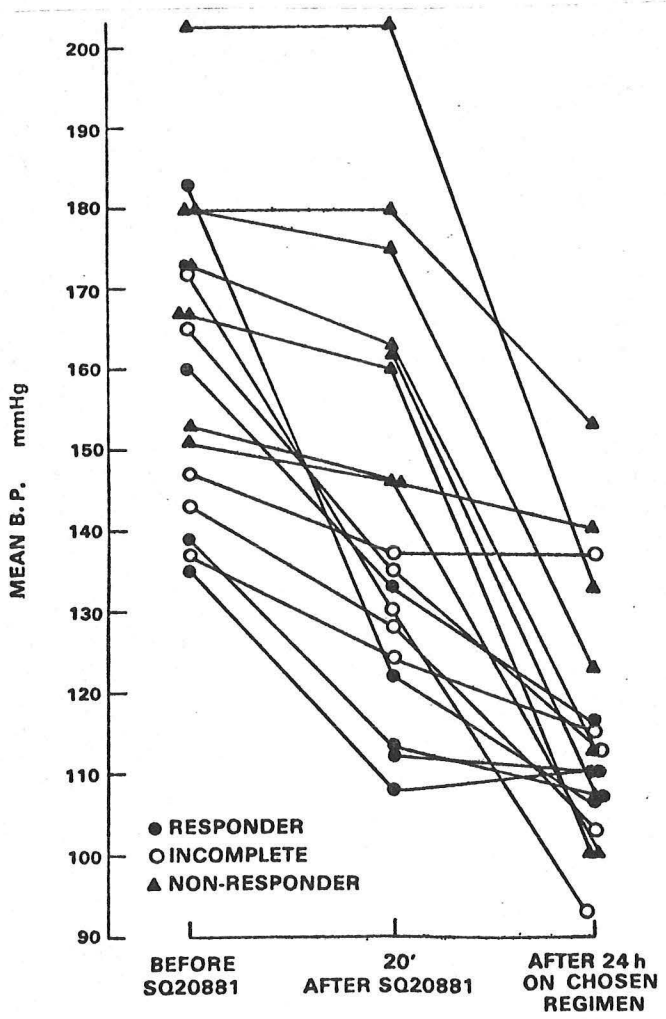


Figure 28: Decrease in mean blood pressure (BP) 20 min after intravenous injection of SQ 20881, 1 mg/kg body weight, in 18 hypertensive patients.

2. Prazosin. Prazosin is an alpha receptor blocking agent that reduces the blood pressure by inhibiting the neural transmission at the post-synaptic alpha receptors. There have been reports of successful treatment of severe hypertension by the administration of large oral doses of Prazosin (117), (Table 32). In this study,

patients who responded to oral Prazosin did not have any prior exposure to the drug, whereas nonresponders were already on maintenance Prazosin therapy. These observations indicate that initial exposure enhances the hypotensive effect and a less satisfactory blood pressure response is likely in patients who are already on maintenance prazosin therapy. These observations correspond with the so-called first dose phenomenon (first-dose hypotension), that has been noted in some patients receiving prazosin (118). Although these results are interesting, they are based upon a limited number of data. So, prazosin therapy should still be considered as experimental in hypertensive emergencies.

Table 32

BP RESPONSE AFTER SINGLE ORAL DOSE OF PRAZOSIN (5.4 mg)

	BASELINE	1-2 HRS	3-4 HRS
SYSTOLIC	194	156	145
DIASTOLIC	121	101	92

3. Labetalol. Labetalol is a combined alpha and beta receptor blocking agent available for the treatment of hypertension in the United Kingdom. This drug has been used in the treatment of hypertensive emergencies by both parenteral and oral routes. Figure 29 shows the response of patients with severe hypertension to oral administration of Labetalol (119). As evident, sustained control of blood pressure was maintained for 24 hours with a single administration of this unique agent. This drug is not available for general use in this country and presently is being evaluated only on an experimental basis. Nevertheless, this form of therapy offers an alternative to the present ways of treating hypertensive emergencies.

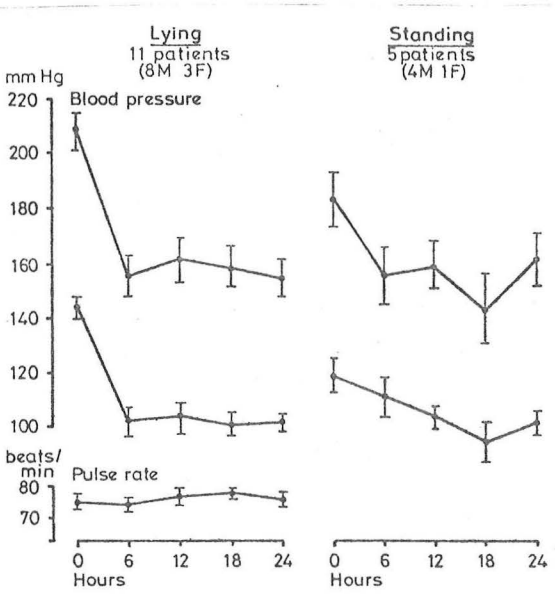


Figure 29: The initial 24-hour period of treatment with oral labetalol in severe hypertension.

4. Minoxidil. This agent is a powerful direct vasodilator and has been successfully used in the treatment of refractory or severe hypertension. Because of its rapid onset of action and sustained duration, this drug has been used for the treatment of hypertensive crises (120). These results are indeed encouraging since they may pave the way for substitution of parenteral agents. Prospective studies are needed before general recommendations are given about the use of minoxidil in hypertensive crises.

5. Intravenous clonidine. In a select group of patients who presented with various types of hypertensive emergencies, intravenous administration of clonidine successfully lowered the blood pressure tp desirable levels (121), Figure 30. Although the blood pressure reduction in these patients was satisfactory, because of the depressant effects of clonidine on the central nervous system, it is unlikely that this form of therapy will gain wide acceptance. Moreover, the intravenous clonidine (as opposed to oral administration) can potentially elevate the blood pressure transiently as a result of peripheral alpha receptor stimulation and this effect, although momentary is not desirable in patients who are already in hypertensive crisis. I.V. clonidine is not available in the United States.

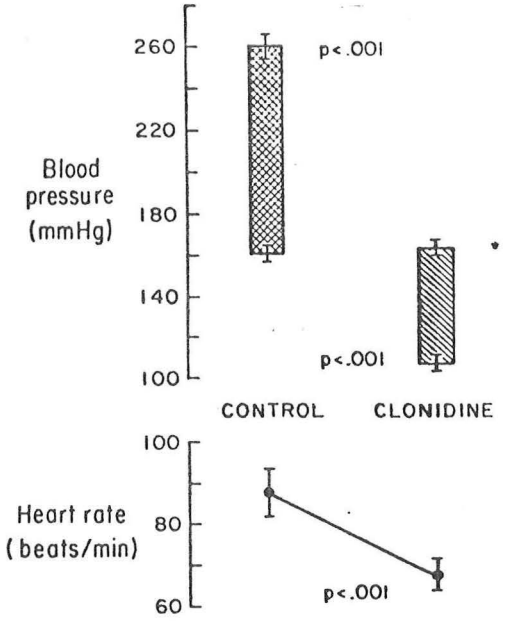


Figure 30: Effect of clonidine on systolic and diastolic blood pressures and heart rate (mean ± S.E.M.) in all patients at the end of intravenous treatment (N = 19).

6. Oral clonidine loading. Oral clonidine, when given in incremental doses has been shown to cause appreciable reduction in blood pressures of patients presenting with severe hypertension (122,123). The results of an ongoing study from this institution are shown in Table 33. Although this form of therapy may be suitable for a few patients because of the convenience of avoiding parenteral agents, one should consider the sedative effects of clonidine which may interfere with the neurological status of patients presenting with severe hypertension. Further studies are necessary to ascertain the role for oral clonidine loading in the treatment of severe hypertension.

Table 33

ORAL CLONIDINE IN SEVERE HYPERTENSION

NO. OF PATIENTS	18
INITIAL BLOOD PRESSURE (AVERAGE)	210/140
FINAL BLOOD PRESSURE (AVERAGE)	151/102
TIME REQUIRED TO REACH FINAL DBP 105 mm Hg OR LESS	5.40 HRS/PT
AVERAGE CLONIDINE DOSE	0.4 MG

OTHER AGENTS

Hydralazine hydrochloride. Hydralazine hydrochloride has been successfully employed in the treatment of severe hypertension (124,125). Its hypotensive action results form the direct relaxation of the vascular smooth muscle and is accompanied by reflex increases in cardiac output, stroke volume and heart rate. The increase in cardiac output as a result of the reflex stimulation has been associated with precipitation of angina pectoris. Intramuscular or intravenous administration of hydralazine results in an unpredictable but definite fall in blood pressure. In the treatment of hypertensive emergencies, the initial dose should be 10 to 20 mg. The onset of the hypotensive effect occurs within 10 to 30 minutes and duration of action ranges from 3 to 9 hours. The dose and the frequency of administration necessary to control the blood pressure are highly variable. The delayed onset and unpredictable degree of hypotensive effect present difficulties in titration. Nevertheless, hydralazine has been, and continues to be, successfully employed in the treatment of severe hypertension, especially eclampsia. The sodium and water retention that occur with the use of this direct vasodilator can be overcome by the use of a diuretic and the reflex increases in the cardiac output and heart rate can be minimized by the administration of a beta adrenergic blocking agent.

Although effective in controlling severe hypertension, this drug has been largely supplanted by one of the more parenteral agents that have been discussed.

THE TRANSITION TO ORAL THERAPY

Oral antihypertensive agents should be administered as soon as the patient is able to take them but only after the patient's presenting manifestations have either cleared or been stabilized. Institution of oral antihypertension agents at the earliest possible time is necessary to avoid the inconvenience of parenteral injections after the hypertension has been controlled. In most patients this is done by the administration of a diuretic and an adrenergic blocker with or without a vasodilator such as hydralazine. In patients recovering from acute cerebrovascular accident or hypertensive encephalopathy, one should not use centrally acting agents such as methyldopa or clonidine because of their sedative effects. One of the common errors in managing hypertensive crisis is to prematurely introduce the oral drugs, which should be given gradually rather than abruptly substituted for potent intravenous medications. Another common error is the failure to monitor the standing blood pressure in a convalescing patient who has been receiving potent antihypertensive agents in the supine position. This point should be emphasized and whenever possible, standing blood pressure should also be taken during the transition to oral therapy so that supine normotension does not transform into postural hypotension.

GENERAL APPROACH TO THE MANAGEMENT AND CONCLUSIONS

The most important consideration in the treatment of hypertension emergencies is to assess the patient's clinical state and ascertain whether the patient's condition truly warrants emergency management with parenteral agents or only just further intensification of his previous therapy. Once the diagnosis of a hypertensive crisis is made, the management should be ideally carried out in an intensive care unit with continuous monitoring of the blood pressure, urine volume and cardiac rhythm. The level to which the blood pressure should be lowered varies with the type of hypertensive crisis and should be strictly individualized; there is no predestined arbitrary level which will be the goal of therapy. The complications of therapy, namely hypotension and ischemic brain damage have occurred in patients who are given multiple potent antihypertensive drugs in large doses <u>without</u> adequate hemodynamic monitoring (126,127). Such catastrophes can and should be avoided by gentle lowering of blood pressure and individualization of therapy.

The relatively asymptomatic patient who might present with severe hypertension, for example with a diastolic BP 130-140 mm Hg, should not be treated with parenteral drugs; these patients should be assessed on an individual basis and the usual course would be to intensify or alter the previous antihypertensive therapy.

The therapy of hypertensive crises does not end with the normalization of BP, but the physician should probe into possible factor(s) that might have contributed to the precipitous elevation of the blood pressure, such as:

1. Reasons for cessation of drug therapy.
2. Onset and/or progression of renal arterial stenosis.
3. Inadequate antihypertensive therapy.

Physicians should inquire into the reasons for noncompliance with prior antihypertensive therapy and take steps to correct the precipitating event so that recurrence of the crisis can be avoided. For example, if an antihypertensive medication has caused significant side effects that have interfered with the patient's function, mental or physical, the same regimen should not be prescribed again and the choice of antihypertensive therapy should be one that will be more acceptable to the patient.

When a patient presents with hypertensive crisis the possibility of an underlying etiology should be explored depending on the physical and laboratory evidence as illustrated by the following cases.

Case No. 1

EJB, a 52 year old female was admitted to St. Paul Hospital because of severe hypertension. This patient was known to have chronic hypertension which has been very difficult to control. She was on furosemide 120 mg, clonidine 1.2 mg, Apresoline 200 mg and prazosin 20 mg a day. On this regimen, the patient's blood pressure remained at 180/92 mm Hg on admission. On the fourth hospital day, the patient developed nausea and severe headache. Her blood pressure was found to be elevated to 220/140 mm Hg. Physical examination was remarkable for the presence of papilledema and the clinical diagnosis of hypertensive encephalopathy was made. The patient was treated with a small bolus of diazoxide which reduced her blood pressure to 190/90 mm of mercury in five minutes and this was maintained through the following day.

This patient developed hypertensive encephalopathy in the hospital despite the institution of bedrest, restriction of sodium intake, and intense drug therapy. The worsening of the patient's hypertension and development of encephalopathy made me suspect a possible underlying etiology for her hypertension. The renal arteriogram revealed tight unilateral renal artery stenosis.

Case No. 2

HT, a 56 year old female was admitted to a local hospital with sudden onset of left-sided weakness and she sustained a small stroke involving the right cerebral hemisphere; her blood pressure was 180/100-120 mm Hg. The patient has been under the regular care of a physician and her blood pressures during the previous examinations have all been within the normal range. This patient subsequently had a renal arteriogram which revealed unilateral fibromuscular displasia of the renal artery.

A recent study documents a high incidence of renal artery stenosis in patients presenting with severe hypertension (128), (Table 34). Thus, it seems prudent that in patients who present with acute onset of hypertension and rapid deterioration of blood pressure control, apart from treating the hypertensive crisis, one should look into the possibility of an underlying etiology.

Table 34

RENOVASCULAR HYPERTENSION IN PATIENTS WITH MALIGNANT HYPERTENSION

NO. OF PATIENTS	RENAL ARTERY STENOSIS	RENOVASCULAR HYPERTENSION
123	43 (35%)	28 (23%)

Inadequate medical therapy and poor instructions might contribute to progressive and rapid rise of blood pressures. The point is illustrated in the following case.

Case No. 3

A 48 year old male was admitted to the hospital with the history and clinical examination consistent with acute stroke involving the right middle cerebral artery distribution. There was no previous history of cerebrovascular accidents, but the patient was discovered to have elevated blood pressure five months prior to this incident (180/100 mm Hg) and was started on furosemide 40 mg a day, but unfortunately the patient was not instructed about follow-up and response to therapy was not assessed. A few months later, the patient had an acute stroke.

This case illustrates severe hypertension resulting in a morbid event, due to insufficient antihypertensive therapy.

True hypertensive crises are uncommon and the physicians should not overreact to elevated blood pressures that do not constitute emergencies. The conditions described here comprise complex and urgent clinical problems. The term "hypertensive crisis" implies an elevation of blood pressure severe enough to cause dysfunction of vital organs if the blood pressure is not reduced immediately. In some cases it is not only the absolute level of the blood pressure, but also the rapidity of rise in blood pressure that determines the gravity of the situation. There are some conditions which are categorized as hypertensive emergencies, not because of the height of the blood pressure, but because coexisting complications make even moderate hypertension dangerous. Potent antihypertensive drugs are available for rapid reduction of blood pressure. Before using these drugs, the physician should assess the neurological and hemodynamic status of the patient as well as the possible hemodynamic effects of the drugs on the patient. Basic understanding of the mechanism of action and the possible adverse effects is vital to the proper application of parenteral antihypertensive agents. Familiarity with the natural history, prognosis, pathophysiology, and hemodynamic determinants of hypertensive emergencies is invaluable in the rational approach to hypertensive crises. Perhaps the greatest challenge lies in our ability to prevent the occurrence of hypertensive crises by identifying and tackling the possible precipitating factors.

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