INTERNAL MEDICINE GRAND ROUNDS

HYPERTENSIVE CRISES

- CLINICAL RECOGNITION AND THERAPY

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I. INTRODUCTION - WHAT IS A HYPERTENSIVE CRISIS?

C.W., a 24 year old white male, was referred because of severe hypertension noted during a routine physical examination. Initial blood pressure readings in his physician's office were 200/150 mm Hg X 2; 24 hour ambulatory blood pressure recordings demonstrated that almost every single blood pressure was > 200/140 mm Hg, several were > 210/150 mm Hg. When I saw him, his blood pressures were 210/146 mm Hg and 200/150 mm Hg. Physical examination was completely normal. Fundi - normal, no cardiomegaly, EKG - normal, routine blood tests including renal function - normal. Patient was asymptomatic. This is not a hypertensive crisis. Patient was admitted to the floor for the treatment of hypertension with oral medication. Work-up for secondary causes was negative.

J.G., a 32 year old black female with known essential hypertension, was admitted to the hospital with headache and lethargy. Blood pressures were 200-210/150 mm Hg. Fundi revealed ? papilledema. No focal neurological deficits were noted. Patient was transferred to ICU to receive I.V. labetalol infusion. Within hours, patient felt better after the blood pressure dropped to 150/100-110 mm Hg. This is hypertensive crisis.

Despite the high prevalence of hypertension in the community, hypertensive crises occur only infrequently. The incidence of hypertensive crises has decreased significantly in the last 25 years, probably due to the widespread use of anti-hypertensive drugs. It is estimated that no more than 1% to 2% of hypertensive patients develop hypertensive crises (Kincaid-Smith, 1980). Hypertensive crises usually develop in patients with chronic hypertension but may also occur in patients with newly discovered or short duration of hypertension. In the previously normotensive individuals, acute elevations in arterial pressure cause complications to a greater degree at any given level of blood pressure than in those with chronic hypertension. In the management of hypertensive crises, prompt therapy should take precedence over diagnostic studies. Valuable time should not be lost in the pursuit of an etiology. The complications of hypertensive crisis are largely reversible but the degree of reversibility depends on how soon appropriate treatment is instituted.

Any form of hypertension may be associated with the development of hypertensive crisis, the chief determinant being the level of blood pressure rather than the etiology of hypertension. A major factor in the development of hypertensive crisis is the abruptness with which the blood pressure rises, since this fact seems to be more important than the absolute level of blood pressure under certain clinical situations - e.g., onset of hypertension as in children with acute glomerulonephritis, toxemia of pregnancy, and drug induced hypertension. In some clinical circumstances immediate reduction of blood pressure is indicated not because of its absolute level but because the coexisting complications may make even moderate hypertension dangerous, e.g., aortic dissection, acute left ventricular failure.

Hypertensive crises are conveniently categorized into emergencies and urgencies (Tables 1 and 2). Hypertensive emergencies carry poor prognosis unless the blood pressure is reduced quickly, whereas, hypertensive urgencies pose less immediate danger, yet they may become emergencies if the blood pressure is not vigorously controlled. Hypertensive emergencies typically constitute conditions in which the blood pressure should be reduced in a few hours, whereas, in hypertensive urgencies, blood pressure reduction can be accomplished in several hours or days. There is no arbitrary level of blood pressure separating hypertensive emergencies and urgencies; although, in the former, the blood pressure levels tend to exceed 200/130 mm Hg.

Table 1: HYPERTENSIVE EMERGENCIES - EXAMPLES
Accelerated/Malignant Hypertension*
Hypertensive Encephalopathy
Acute Left Ventricular Failure
Acute Aortic Dissection
? Intracranial Hemorrhage
Pheochromocytoma Crisis
MAO Inhibitor + Tyramine Interaction
Eclampsia
Substance/Drug Induced Acute Hypertension
*Can also be considered as an urgency.

Table 2: HYPERTENSIVE URGENCIES - EXAMPLES
Accelerted/Malignant Hypertension*
Severe Hypertension Associated with Coronary Arter Disease
Severe Hypertension in the Kidney Transplant Patient
Preoperative Hypertension
Hypertension Associated with Burns
*Can also be considered as an emergency

II. ACCELERATED AND MALIGNANT HYPERTENSION

The most striking difference between uncomplicated and accelerated/malignant hypertension is the presence of acute vascular lesions in the kidney and in other target organs in the latter (Kincaid-Smith, 1980). Accelerated hypertension is identified by the presence of severe retinopathy (without papilledema) - exudates, hemorrhages, arteriolar narrowing, and spasm. Malignant hypertension, an extension of the accelerated form, is distinguished by the presence of papilledema. Both the accelerated and malignant forms of hypertension are associated with clinical evidence of severe vascular injury to the kidney and other target organs. Prior to the availability of antihypertensive therapy, malignant hypertension ran a short clinical course culminating in renal failure and death. With proper antihypertensive therapy, however, the prognosis has improved with more than 90% of the treated patients surviving more than 5 years and there is no significant difference in the course of accelerated or malignant disease, suggesting that the two be considered part of the same process (Ahmed et al, 1986).

Pathogenesis

What transforms a previously stable hypertensive state to a "malignant" course? The level of blood pressure, although a feature, does not explain the onset of malignant hypertension since there is considerable overlap between the blood pressure levels in patients with uncomplicated and malignant hypertension (Kincaid-Smith, 1981) (Figure 1). Stimulation of various vasoactive mechanisms - renin-angiotensin, catecholamines, vasopressin, and kallikrenin-kinin system - have been implicated in the genesis of malignant hypertension. Yet no convincing evidence has been presented to relate the vascular pathology of malignant hypertension to any of these neurohumoral derangements. Cigarette smoking has been noted as enhancing the risk of malignant hypertension (Isles, 1980; Bloxham et al, 1979). Immunological abnormalities also have been found in patients with malignant hypertension (Forsberg and Low, 1983; Gubrandsson et al, 1981). The arteriolar lesions responsible for the clinical manifestations and course of malignant hypertension are found in many organs including kidney, brain, heart, intestine, and pancreas (Hepinstall, 1953; Ljunquist, 1962).

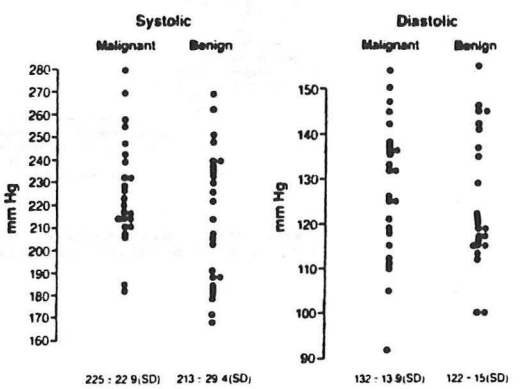


Figure 1: Systolic and diastolic blood pressure levels in age- and sex-matched patients with severe benign and malignant hypertension. [From Kincaid-Smith, 1981].

The consequence of obstructive vascular lesions is a decrease in perfusion to the affected organs, with the kidney bearing the main damage. Two different renal lesions have been described in malignant hypertension: proliferative arteritis and fibrinoid necrosis. The combination of these lesions is also referred to as hyperplastic arteritis, fibrinoid intimal hyperplasia, and musculo-mucoid intimal hyperplasia. Fibrinoid necrosis presumably results from the leakage of fibrin and other plasma elements into the arteriolar wall resulting in obstruction, thus compromising the function of the organ involved - usually the kidney (Ramos, 1984). The precise link between the blood pressure level and arteriolar lesions is not established. It has been suggested that vascular permeability increases as a result of alternating contracted and dilated segments in the arterial vessels and with the treatment of hypertension, these abnormalities are eliminated. These sausage-string changes in renal arterioles induce turbulence leading to endothelial, separation, damage, platelet deposition, thromboxane release, myointimal proliferation - all resulting in vascular obstruction (Kincaid-Smith, 1991) (Figure 2).

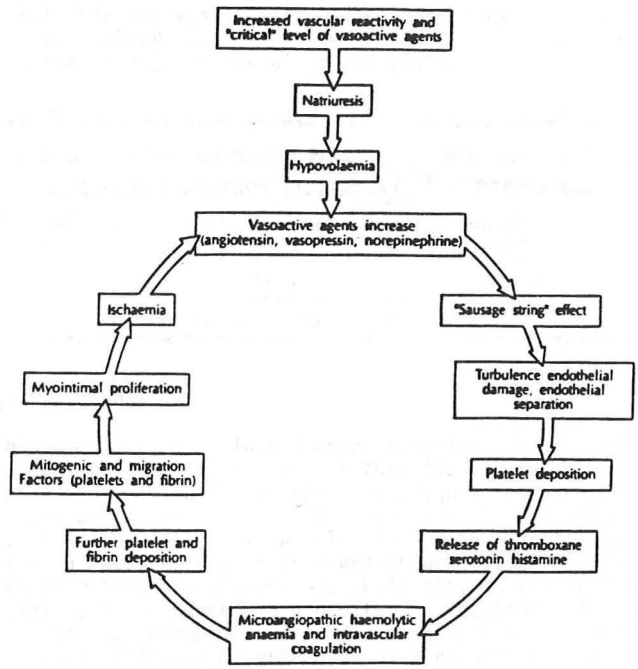


Figure 2: Schematic representation of the factors which may contribute to the vicious circle in malignant hypertension. [From Kincaid-Smith, 1991].

Plasma renin activity is markedly high in malignant hypertension. One mechanism postulates an initial spontaneous sodium loss and volume depletion as the most likely cause (Mohring et al, 1975). In experimental malignant hypertension, the lumen of the efferent renal arteriole remains unchanged whereas the caliber of the afferent arteriole increases in size. Angiotensin sensitivity is augmented in the afferent arteriole whereas the efferent arteriole shows hypersensitivity to both norepinephrine and angiotensin. This differential in sensitivity to circulating levels of angiotensin increases intra-glomerular pressure and promotes natriuresis which in turn stimulates the release of renin, vasopressin, and norepinephrine - and, thereby, initiates a vicious cycle. Initial weight loss, a phenomenon observed in malignant hypertension, may be due to the loss of salt and water. The course of malignant hypertension has been curtailed experimentally and clinically by administering a saline load (Mohring et al, 1976; Kaneda et al, 1980). It appears, therefore, that the renin-angiotensin system may play some role in the pathogenesis of malignant hypertension. The renin-angiotensin system is obviously also involved in hypertensive emergencies caused by renovascular disease. In one series, renal artery stenosis was detected in 35% of 123 patients with malignant hypertension (Davis et al, 1979) (Table 3).

TABLE 3: RENOVASCULAR HYPERTENSION IN PATIENTS WITH ACCELERATED/MALIGNANT HYPERTENSION*

No. of Patients	Renal Artery Stenoses	Renovascular Hypertension
123	43 (35%)	28 (23%)

*From Davis BA, et al, 1979

Clinical Manifestations

The blood pressure level in malignant hypertension is usually quite high with diastolic levels often greater than 130-140 mm Hg but the degree of blood pressure elevation is not the only diagnostic factor. The elevation of the blood pressure has to occur abruptly, and most importantly, it is the extent of vascular injury that determines the nature of clinical manifestations (Ram and Khoury, 1992) (Table 4). Headache with or without coexisting encephalopathy is the most common symptom. Usually, the headache is occipital in location and more intense in the morning hours. Weight loss, as discussed earlier, may occur in some patients with malignant hypertension as a result of salt and water loss. A majority of patients with malignant hypertension report visual symptoms ranging from blurring to blindness. Drowsiness and altered mental status are commonly observed in patients with malignant hypertension. Any worsening of these symptoms may indicate progression to encephalopathy or other cerebral malfunction.

TABLE 4: CLINICAL MANIFESTATIONS OF ACCELERATED OR MALIGNANT HYPERTENSION
1. Marked elevation of BP
2. Malaise; weight loss
3. Headache
4. Retinopathy
5. Renal failure (azotemia, proteinuria hematuria, etc.)

Congestive heart failure can be a presenting feature of malignant hypertension as a direct consequence of left ventricular dysfunction or due to volume retention from associated renal insufficiency. Azotemia, a common feature of malignant hypertension, may be associated with proteinuria. Renal function deteriorates rapidly without proper therapy. Even with appropriate treatment, renal function may decline at times due to reduced renal perfusion. Although hypertension can result from chronic renal disease, renal failure in patients with malignant hypertension is a result rather than the cause of severe hypertension. Anemia is a common finding in malignant hypertension. The degree of anemia may give a clue as to the proximate cause - severe anemia suggests underlying chronic renal disease whereas modest degrees may reflect microangiopathic hemolysis.

The diagnosis of accelerated and malignant hypertension can be made at the bedside on the basis of history and clinical examination. Simple investigations such as chest X-ray, EKG, CBC, BUN, creatinine, electrolytes, and urinalysis are sufficient for the initial management of malignant hypertension (Ram, 1983; Ram, 1988; Ram and Heller, 1988).

Management

Patients with accelerated/malignant hypertension should be treated in the hospital as the goal is not simply to lower the blood pressure but to monitor, stabilize, and reverse the damage to target organs and to exclude reversible causes. Preferably, the patients should be treated in an intensive care unit. However, in the absence of significant target organ dysfunction, they can be managed safely on the wards.

Although sodium restriction was successfully used to treat malignant hypertension decades ago (Kempner, 1944), as discussed earlier, sodium wasting may be a feature of this condition. Therefore, sodium restriction is not necessary during early treatment unless there is evidence of fluid overload. Similarly, the need for immediate diuretic therapy must be individualized. Diuretic therapy may be needed subsequently to potentiate the hypotensive effects of certain vasodilators such as nitroprusside and hydralazine; therefore, it is a common clinical practice to co-administer

(intravenous) furosemide with these drugs. However, diuretics should not be used unnecessarily since volume depletion in malignant hypertension can further aggravate the pathophysiological mechanisms.

Sodium nitroprusside is a suitable drug for immediate reduction of severe hypertension. The details of its use will be discussed later. Thiocyanate, a product of nitroprusside metabolism accumulates in patients with renal failure and thiocyanate toxicity can occur in patients receiving high or prolonged infusions of nitroprusside. This problem is rarely encountered unless the infusion is maintained beyond 48-72 hours. Prompt reduction in blood pressure can similarly be accomplished by bolus injections or slow infusion of diazoxide or labetalol. Trimethapan offers some advantages in patients with acute aortic dissection by virtue of its ability to decrease the force and velocity of left ventricular contraction. Oral medications should be started once the blood pressure has been stabilized at a desired level and only then can the patient be weaned off the intravenous drips.

While parenteral therapy is widely used in the initial treatment of malignant hypertension, various oral therapies can also be successfully used. Captopril, minoxidil, clonidine, prazosin, labetalol, and nifedipine have all been used for initial treatment of malignant hypertension. The choice between oral and parenteral therapy depends on the monitoring facilities, condition of the patient, and coexisting complications. Once the blood pressure is brought to safe levels, long-term therapy must be initiated with appropriate agent(s) based on the renal, cardiac, and neurological status of the patient.

III. HYPERTENSIVE ENCEPHALOPATHY

Hypertensive encephalopathy is one of the most serious complications of severe hypertension. Although encephalopathy occurs mainly in patients with malignant hypertension, it can also complicate hypertension of short duration. Hypertensive encephalopathy should be quickly recognized and effectively treated since it carries a poor prognosis if untreated but is rapidly reversible with proper treatment (Ram, 1978). The clinical manifestations of hypertensive encephalopathy are precipitated not only by severity of blood pressure elevation but also by the abrupt onset of hypertension in a previously normotensive individual. It is generally recognized that hypertensive encephalopathy occurs more frequently when the hypertension is complicated by renal insufficiency than when kidney function is normal. The full clinical syndrome may take 12 to 48 hours to develop (Gifford and Westbrook, 1974; Cuneo and Caronna, 1977; Ram, 1991).

The pathogenesis of hypertensive encephalopathy has been extensively studied and divergent opinions exist as to its mechanisms. It is generally believed that encephalopathy is precipitated by the derangement in cerebral autoregulation. Normally, cerebral blood flow (CBF) remains relatively constant despite wide variations in systemic blood pressure (Figure 3). This remarkable constancy is accomplished by autoregulation of the cerebral blood flow; in the face of marked elevation in systemic

blood pressure, cerebral arterioles constrict; with a fall in blood pressure, cerebral arterioles dilate to maintain adequate cerebral blood flow. In hypertensive encephalopathy, however, cerebral autoregulation is deranged such that cerebral blood flow is seriously affected. It was originally proposed that in hypertensive encephalopathy there is over-regulation (exaggerated vasoconstriction) but it is now believed that it is the lack of vasoconstriction which may play a central role in the pathogenesis of hypertensive encephalopathy (Strandgaard et al, 1976). The inability of cerebral arterioles to constrict results in hyperperfusion. Breakthrough of circulatory response with a consequent increase in cerebral blood flow may result in cerebral edema (Figure 4).

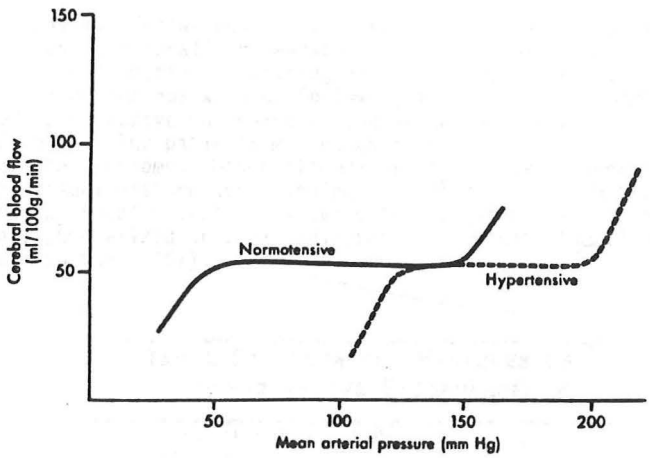


Figure 3: Cerebral blood flow autoregulation in normotensive and hypertensive individuals. [Modified from Strandgaard S, et al. Autoregulation of brain circulation in severe arterial hypertension. Br Med J 1973;1:507].

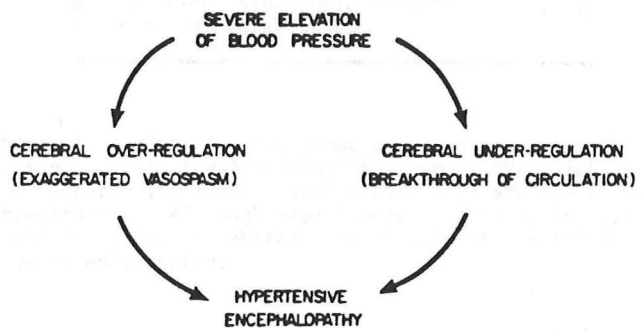


Figure 4: Pathogenetic mechanisms of hypertensive encephalopathy. [From Ram CVS, 1978].

Clinical Features

M.H., a 34 year old black male with a history of chronic hypertension and renal insufficiency, presented to ER with the chief complaints of severe headache and nausea of 2 days duration. His admitting blood pressure was 220/148 mm Hg; physical examination showed no focal neurological deficits but papilledema was present. Patient was admitted to ICU for nitroprusside infusion. His symptoms improved along with a reduction in blood pressure over a 24-48 hour period. Oral therapy with nifedipine-XL and labetalol was begun and patient was transferred to the floor. This case represents classical hypertensive encephalopathy.

Clinical manifestations of hypertensive encephalopathy are shown in Table 5. Severe generalized headache is a prominent clinical symptom. Neurological dysfunction consisting of confusion, somnolence, and stupor may appear simultaneous with or following the onset of headache. If untreated, progressive worsening of the sensorium occurs culminating in coma and death. The patients may be quite restless during the initial stages of the syndrome. Other clinical features may include projectile vomiting, visual disturbances ranging from blurring to frank blindness, and transient focal neurological deficits. Sometimes (especially in children), generalized or focal seizures may dominate the clinical picture (Still and Cotton, 1967).

TABLE 5: CLINICAL FEATURES OF HYPERTENSIVE ENCEPHALOPATHY

1.	Marked elevation of BP
2.	Headache
3.	Nausea, vomiting
4.	Papilledema
5.	Visual complaints
6.	Transient neurologic deficits (seizures)
7.	Altered mental status

On physical examination, the blood pressure is invariably elevated but there is no certain level of blood pressure above which encephalopathy is likely to occur. The fundi reveal generalized arteriolar spasm with exudates/hemorrhages. Although papilledema is present in most patients with this complication, its absence should not exclude the diagnosis of hypertensive encephalopathy.

Diagnosis

When a patient with poorly controlled hypertension presents with severe headache, altered mental status, papilledema, and variable

neurological deficits, the most likely initial diagnosis is hypertensive encephalopathy which, of course, must be distinguished from other acute neurological complications of hypertension such as cerebral infarction or hemorrhage and uremic encephalopathy (Ram, 1982) (Table 6). A thorough but quick evaluation of the patient should be carried out to consider these differential diagnoses (Table 7). The possibility of reflex elevation of systemic blood pressure in response to cerebral ischemia should be considered the differential diagnosis. The only definitive criterion to confirm the diagnosis of hypertensive encephalopathy is a prompt response of the patient's condition to antihypertensive therapy. The syndrome reverses within one to twelve hours with appropriate control of hypertension.

TABLE 6: DIFFERENTIAL FEATURES OF HYPERTENSIVE ENCEPHALOPATHY AND CEREBROVASCULAR ACCIDENTS

	EVOLUTION	HEADACHE	CONSCIOUSNESS	SIGNS
Hypertensive encephalopathy	Subacute (12-48 hr)	Severe Generalized Recent onset	Initially clear but progresses to coma	Nausea and vomiting Visual disturbance Seizures Transient neurologic deficits
Cerebral infarction	Rapid (few min to 6 hr)	None or mild	Inattentive Coma very rare	Fixed neurologic 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 and secondary involvement	Fever Stiff neck Aphasia Cranial nerve palsies

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
6. Acute encephalitis
7. Toxic encephalopathy

Management

Once the diagnosis of hypertensive encephalopathy is suspected, the blood pressure should be lowered rapidly to near normal levels yet the diastolic blood pressure should probably remain at or slightly above 100 mm Hg. Rapid reduction in the blood pressure produces prompt, dramatic, and significant relief of symptoms of hypertensive encephalopathy. The patient should be treated in an intensive care unit. The most important goal of therapy is to prevent permanent neurological damage. A useful and dependable drug in this situation is sodium nitroprusside. Specific details concerning this and other antihypertensive agents are discussed elsewhere. Although potent orally effective agents like minoxidil, nifedipine, or captopril can control severe hypertension, parenteral drugs are preferred in treating a potentially dangerous condition such as hypertensive encephalopathy.

IV. SEVERE HYPERTENSION AND CEREBROVASCULAR ACCIDENTS

Patients with acute stroke and severe hypertension pose a challenging management dilemma. When intracerebral pressure rises as a result of hemorrhage or thrombotic infarction, cerebral blood flow may no longer be under normal autoregulation. Therefore, a reduction in the systemic blood pressure may conceivably further compromise cerebral blood flow. Conversely, persistent severe hypertension may worsen the stroke process. In many patients with acute stroke, initial hypertension may resolve spontaneously within 48 hours (Wallace and Levy, 1981) (Figure 5). There are no definitive data in the literature that will provide the practicing physicians with a standard approach in managing these patients.

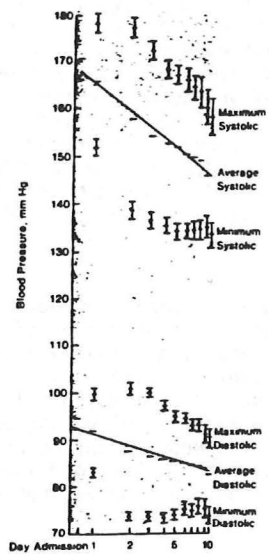


Figure 5: Mean daily maximum and minimum, systolic and diastolic blood pressure, ±SEM for patients with hemispheric thrombotic infarcts. The regression lines are fitted to the average systolic and diastolic pressure values (midpoint between means of extreme pressures). [From Wallace & Levy, 1981].

Is Antihypertensive Treatment Harmful?

Several important 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 (Hofft and Reis, 1970). 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. 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 studies to guide the appropriate therapeutic approach.

Is Treatment of Hypertension Beneficial?

Intracerebral hemorrhage is a devastating complication of chronic hypertension with a high mortality (Matsumoto et al, 1973). In such a catastrophic condition, 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 (Whisnant, 1968) showed that 89% would favor acute antihypertensive treatment in such patients in the hope of preventing further hemorrhage. In one study, there was a significant benefit of antihypertensive therapy in managing hypertensive cerebral hemorrhage (Meyer and Bauer, 1962). 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. In patients with subarachnoid hemorrhage, there is evidence suggesting a higher rate of rebleeding and mortality if the systolic blood pressure is greater than 160 mm Hg. However, it is the general opinion that there is no meaningful role for antihypertensive therapy in patients with subarachnoid hemorrhage (Heros et al, 1983).

In contrast to 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 cerebrovacular accidents. However, based on the pathogenesis of these conditions, especially intracerebral hemorrhage and, 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 100 mm Hg, usually. In any event, the reduction should be no more than 20% of the baseline blood pressure level (Lavin, 1986). Hazards of unwarranted antihypertensive therapy have been well documented (Britton et al, 1980; Barry, 1989). A smooth and desired level of blood pressure control is only achieved with a short-acting antihypertensive drug. Drugs with a central mechanism of action like reserpine, clonidine, and methyldopa, should be avoided as they may interfere with the neurological evaluation of the patient.

V. 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 (Hirst et al, 1958). Dissection of the aorta is the most common acute disease of the aorta and occurs at the rate of around five to ten cases per million population each year. In addition to being the most common acute catastrophe involving the aorta, the acute dissection is also the most lethal condition. Most untreated patients with acute aortic dissection die within one year. Most of the deaths occur within 2 weeks (Crawford, 1990).

The primary event in aortic dissection is rupture of the intima with subsequent exposure of the media to intraluminal pressure of the aorta. The initial primary event is an intimal tear which separates the layers of the aorta causing a classic "double-barrel" aorta. The pathological lesion responsible for the dissection is cystic medial necrosis. Factors associated with cystic medial necrosis include hypertension, aging, coarctation, pregnancy, and connective tissue diseases such as Marfans or Ehlers-Danlos syndrome. A breach in the intima causes separation within the medial layers of the aorta. The false lumen is filled with blood or clot that can propagate in an antegrade or retrograde direction.

It is clear that an association exists between hypertension and aortic dissections (Roberts, 1980). Hemodynamic forces cause injury to the intima leading to changes in the media. Hypertension may have a direct weakening effect on the aortic media. In order to understand the clinical manifestations and management principles, it is necessary to consider the morphological classification of aortic dissection:

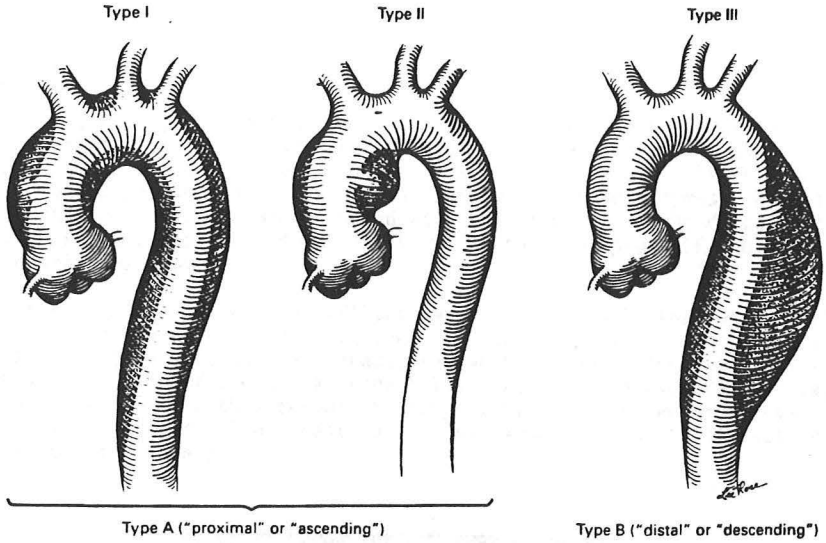


Figure 6: The DeBakery (top) and Stanford (bottom) systems for classification of aortic dissection.

DEBACKEY'S CLASSIFICATION OF DISSECTING ANEURYSMS

Type 1: Begins in the ascending aorta and extends at least into the arch and possibly through the descending aorta.

Type 2: Dissection is localized to the ascending aorta only.

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.

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

Clinical Features

E.B., a 53 year old black male, was admitted to the hospital because of "tearing" pain in the back and chest. Patient was known to have chronic hypertension X 15 years with inadequate follow-ups. EKG showed LVH, chest X-ray showed a widened mediastinum. Cardiac enzymes - normal. CT of the chest and abdomen revealed aortic dissection of the descending aorta. Patient was treated medically (with labetalol plus ACE inhibitor) and discharged from the hospital.

Acute aortic dissections 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 an elderly male with a chronic history of hypertension who presents with severe and persistent chest pain. The symptoms of acute dissection are listed in Table 8.

Table 8: SYMPTOMS OF ACUTE 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. 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 dissection (Hume, 1963; Levinson et al, 1950). 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.

Physical findings in acute aortic dissection can be mani-fold (Table 9). Table 10 is a lists of conditions which should be included in the differential diagnosis of acute aortic dissection.

Table 9: Physical Findings in Acute Aortic Dissection

1. Hypertension
2. Tachycardia or bradycardia
3. Deficiency of pulses
4. Cardiac tamponade
5. Unilateral or bilateral jugular venous distention
6. Cardiomegaly
7. Pericardial friction rub
8. Hemiplegia, paraplegia
9. Paralytic ileus

Table 10: Differential Diagnosis of Acute Aortic Dissection

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

Diagnosis

The clinical diagnosis of aortic dissection is based upon a high index of suspicion and the presenting features. Once the diagnosis is suspected, immediate medical therapy should be implemented pending the diagnostic tests. A chest X-ray may show a recent widening of the mediastinum but unless compared with the previous films, it is not a useful study.

2-D echocardiography, transesophageal echocardiography, magnetic and resonance imaging (MRI) have all been utilized to diagnose aortic dissection. (Petasnick, 1991; Chan, 1992; Om and Mohanty, 1992; Wilbers et al, 1990). The diagnostic accuracy of these procedures depends on experience of the operators and the facilities. MRI combined with transesophageal or transthoracic echocardiography yields considerable information (Figure 7). However, MRI is only recommended for patients who are hemodynamically stable and who can be transported to the MRI suite. Digital and/or conventional angiography provide more thorough information concerning the anatomy of dissection and the course taken by the dissecting hematoma.

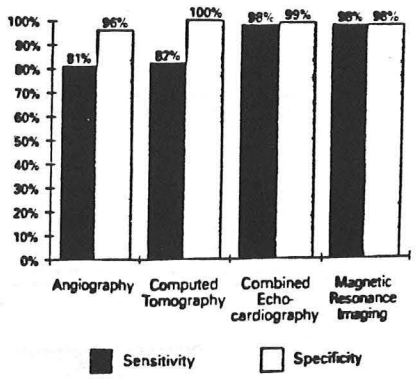


Figure 7: Comparative sensitivity and specificity of various imaging techniques in diagnosing aortic dissection. [From Wilbers et al, 1990].

Initial Management

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. 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 (Ram and Kaplan, 1984). Attempts should be made to decrease the dp/dt with a suitable agent; drugs that reflexly stimulate the heart should be avoided.

The concept has been proposed that the driving force 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 objective of appropriate antihypertensive therapy is to reduce the velocity of myocardial shortening, which can be done with drugs having negative inotropic effects. These physical concepts are critical to our understanding of acute aortic dissection and, more importantly, to the choice of antihypertensive therapy (Figure 8). 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; therefore, it decreases the pulsative 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 (Wheat, 1973). The other options would include labetalol, a combined alpha- and ß-blocking drug or the ultra-short acting ß-blocker, esmolol (Hogan, 1990).

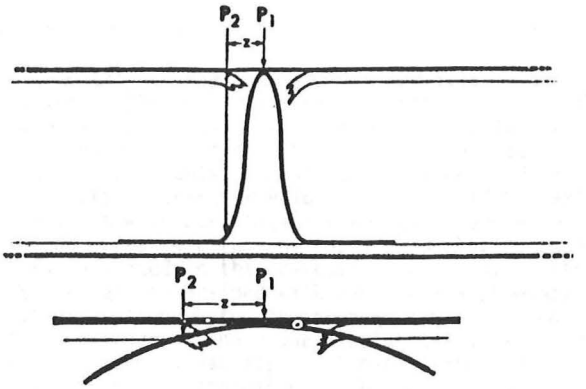


Figure 8: Pulse profile of the aorta. [From Palmer RF: Pharmacologic management of hypertensive catastrophes, in Eliot RB, ed. The Acute Cardiac Emergency. Mount Kisco, NY: Futura Publishing Co., p. 131].

The goal of antihypertensive therapy is to lower the blood pressure to the lowest level tolerated by the patient without causing cerebral, myocardial, or renal hypoperfusion.

Definitive Therapy

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 (Garrett and Ram, 1984). There has been considerable controversy in the literature regarding the surgical versus 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. (Crawford, 1990).

For the patients with uncomplicated distal dissection (Type 3), continuation of chronic medical therapy offers a slight, 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 patient if there is evidence of rupture or vital organ compromise or inability to contain the hematoma with appropriate medical therapy.

VI. ACUTE LEFT VENTRICULAR FAILURE

Severe uncontrolled hypertension may precipitate acute left ventricular failure. The higher the blood pressure, the harder must the left ventricle work. Decreasing the workload of the failing myocardium can improve the cardiac function. In acute left ventricular failure, myocardial oxygen requirements increase due to increased end-diastolic fiber length and left ventricular volume. This could be particularly dangerous in patients with concomitant coronary artery disease. Prompt reduction of blood pressure with a balanced vasodilating agent such as nitroprusside is indicated in this circumstance. Sodium nitroprusside decreases both pre- and after-load with restoration of myocardial function and cardiac output. Although the angiotensin converting enzyme (ACE) inhibitors, by the virtue of their pharmacological actions, may be useful in this situation, there is paucity of clinical experience concerning the therapeutic response to ACE inhibition in patients with acute left ventricular failure. Drugs which increase the cardiac work such a hydralazine and diazoxide should be avoided. Along with the treatment of hypertension, other measures for managing pulmonary edema should be instituted.

VII. SEVERE HYPERTENSION ASSOCIATED WITH ISCHEMIC HEART DISEASE

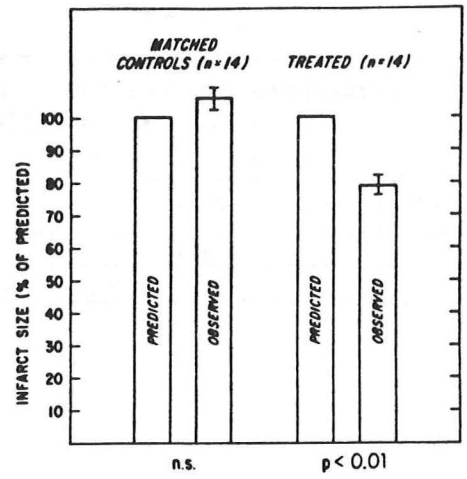


Figure 9: Comparison of infarct size in normotensive controls and in hypertensive subjects after trimethaphan therapy. [From Shell and Sobel, 1974].

Systemic hypertension increases myocardial oxygen consumption by increasing the left ventricular tension. Patients with myocardial infarction and severe hypertension should, therefore, theoretically benefit from blood pressure reduction but there are no conclusive data to prove that treatment is beneficial. Reduction of systemic blood pressure

reduces the cardiac work, wall tension, and oxygen demand and may thus limit myocardial necrosis in the early phase of infarction (Shell and Sobel, 1974) (Figure 9). However, there are conflicting data in the literature about the value of reducing blood pressure (to reduce infarct size) in the absence of pulmonary congestion. Although hypertension usually precedes the onset of chest pain, a marked rise in blood pressure may follow the onset of coronary insufficiency. Therefore, an acute elevation of blood pressure in the setting of acute myocardial infarction may be transient and not harmful (Gibson, 1978), but others have observed that the mortality rate and incidence of cardiac failure were significantly greater in patients with severe systolic hypertension and acute myocardial infarction (Fox et al, 1975) (Table 11). With a reduction in the after-load, the hemodynamic status improves significantly in myocardial infarction (Chatterjee, 1973). Cautious treatment of hypertension in patients with acute myocardial infarction is, therefore, likely to be beneficial. Parenteral agents such as sodium nitroprusside can be used. Diazoxide and hydralazine should be avoided in this situation because of their adverse hemodynamic effects. It must be emphasized that the degree of blood pressure reduction should depend solely on the demonstration of a beneficial hemodynamic response; unnecessary reduction in the blood pressure could compromise an already unstable situation.

TABLE 11: ACUTE MI: OUTCOME IN NORMOTENSIVE AND HYPERTENSIVE SUBJECTS*

	NO. PTS	AGE	PREVIOUS CAD	MORTALITY	CHF	ARRHYTHMIAS
Systolic hypertension	106	58±10	31	13 (12%)	35 (35%)	22 (21%)
Controls	106	57±10	38	2 (2%)	10 (9%)	5 (5%)

* Reproduced, with permission, from Fox K.M. et al, 1975.

VIII. MISCELLANEOUS CONDITIONS

1) Pheochromocytoma Crisis

A patient with pheochromocytoma crisis may present with striking clinical features. The blood pressure is markedly elevated during the paroxysm and the patient may have profound sweating, marked tachycardia, pallor, numbness, tingling, and coldness of the feet and hands. 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 (Ram and Engelman, 1979).

If pheochromocytoma is suspected, the alpha-adrenergic blocking drug, phentolamine, should be given in the dose of 5 to 10 mg intravenously, to be repeated in a few minutes if needed. An alternative to phentolamine would be sodium nitroprusside, but the former is more specific. A ß-blocking drug may be useful if the patient has a concomitant cardiac arrhythmia. Administration of ß-blocking agents should always be preceded by either phentolamine or phenoxybenzamine. If this is not done, ß-blockade can aggravate the unopposed alpha-mediated peripheral vasoconstriction. Labetalol, a combined alpha- and ß-receptor blocking drug has also been successfully used in this condition.

2) Clonidine Withdrawal Syndrome

A hyperadrenergic state mimicking pheochromocytoma crisis has been reported following abrupt discontinuation of the antihypertensive drug, clonidine (Hansson et al, 1973). Clonidine stimulates the alpha receptors in the brain stem, thus reducing peripheral sympathetic activity. When clonidine is abruptly discontinued (especially high doses) or even sometimes rapidly tapered, a syndrome has been noted consisting of nausea, palpitations, anxiety, sweating, nervousness, and headache - along with marked elevation of the blood pressure. In some patients the blood pressure rises beyond the pretreatment level. The probable mechanism of the clonidine withdrawal syndrome is a sudden reemergence of sympathetic activity. The incidence of this syndrome is quite low and in some there is only a rapid return of blood pressure towards the pretreatment level rather than an overshoot (Ram and Engelman, 1979).

Symptoms of clonidine withdrawal can be relieved by reinstitution of clonidine. If there is marked elevation of blood pressure and the patient is experiencing symptoms - such as palpitations, chest discomfort, epigastric discomfort - intravenous administration of phentolamine or labetalol is recommended.

3) Hypertensive Crisis Associated with Drug and Food Interactions: Monamine Oxidase Inhibitors

Patients receiving monamine oxidase inhibitors (MAO) are at risk of developing hypertensive crisis if they should also take drugs such as ephedrine or amphetamines, or foods containing high quantities of tyramine (Table 12). In the presence of an inhibitor of MAO, tyramine and indirectly acting sympathetic amines escape oxidative degradation, enter the systemic circulation, and potentiate the actions of catecholamines. Sympathomimetic amines such as those contained in nonprescription cold remedies can also provoke this response.

TABLE 12: EXAMPLES OF MAO INHIBITORS AND FOODSTUFFS WITH HIGH TYRAMINE CONTENT

MAO Inhibitors	Foods or Substances with High Tyramine Content
Pargyline (Eutonyl)	Chianti wine, some beers
Nialamide (Niamid)	Aged cheese (Cheddar, Brie)
Furazulidone (Furoxone)	Avocados, banas, chocolate
Phenelzine (Nardil)	Chicken liver, fermented sausage
Tranylcypromine (Parnate)	Soy sauce, yeast extract

The hypertensive attack occurs from 1 to 2 hours after intake of the offending agent, with an abrupt onset, and sometimes lasts up to several hours. Typically, the patient feels suddenly ill with headache, sweating, palpitations, and the blood pressure is often elevated to alarming levels. Manifestations of food/drug interaction with MAO inhibitors closely resemble those of pheochromocytoma. Immediate treatment is similar to that of pheochromocytoma crisis (Lippman and Nash, 1990).

4) Hypertensive Crisis Induced by Metoclopramide

Hypertensive crisis induced by metoclopramide has been reported in previously normotensive subjects (Sheridan et al, 1982) and in patients with pheochromocytoma (Abe et al, 1984). The exact mechanism by which metoclopramide, a dopamine agonist, causes the hypertensive response is not known. It could sensitize the vascular endothelium to the pressor effects of catecholamines or cause a release of catecholamines from the adrenal medulla or adrenergic neurons.

5) Severe Hypertension Associated with Erythropoietin

Erythropoietin therapy has been reported to cause hypertension, which can be severe at times (Brown et al, 1990; Raine and Roger, 1991). With the increasing use of erythropoietin, the problem of hypertension in the recipients will likely increase. Erythropoietin therapy can result in the development of hypertensive crisis. The mechanism of erythropoietin induced hypertension are complex and include - elevation of systemic vascular resistance due to blunted hypoxic vasodilation from the correction of anemia, hypervolemia, increased blood viscosity, activation of sympathetic nervous system, etc. As an alternative to antihypertensive therapy, phlebotomy has been shown to lower the blood pressure in patients developing erythropoietin induced malignant hypertension (Fahal et al, 1991).

6) Severe Hypertension Associated with Cyclosporine

Severe hypertension can result from the use of cyclosporine. Routine use of cyclosporine A in the transplant patients has resulted in the development of severe hypertension (Chapman et al, 1987). Possible cause of cyclosporine induced hypertension include augmented sympathetic neuronal activity (Scherrer et al, 1990) and enhanced renin production by the native kidney (Curtis et al, 1983).

Calcium antagonists have proven to be very effective in controlling cyclosporine induced hypertension (Davidson and Rooth, 1991). Whether the therapeutic effect is a non-specific consequence or due to a reversal of cyclosporine induced hypertensive mechanisms by calcium antagonists is not fully understood. Fenoldopam, an experimental drug with dopamine-1 receptor agonistic properties has been shown to reverse cyclosporine induced vasoconstriction in the rat and clinical experience is awaited with this unique drug (Brooks et al, 1990; Elliott et al, 1990).

7) Cocaine Induced Hypertensive Crisis

Cocaine use can cause an abrupt sudden increase in the systemic blood pressure resulting in a hypertensive emergency (Cregler and Mark, 1986). Neurohumoral factors triggered by cocaine likely cause intense vasoconstriction, thus increasing the vascular resistance and the blood pressure level. Sudden rise of blood pressure in a previously normotensive individual may result in serious cardiovascular complications; and cocaine use has resulted in cardiovascular crisis (Barth et al, 1986). The blood pressure should be lowered to safe limits without much delay. Since sympathetic activation may underly cocaine induced hypertension, ß-blockers alone may aggravate the situation due to unopposed alpha-receptor mediated vasoconstriction (akin to other catecholamine excess states such as pheochromocytoma).

8) Severe Hypertension Associated with Head Injury

Patients with head injury may present with marked elevation of blood pressure. The mechanism is likely complex, but may involve the medullary vasomotor centers which, when rendered ischemic, may reflexly elevate the blood pressure (Fink, 1987). Increased intracranial pressure per se may induce certain compensatory cardiovascular changes resulting in hypertension. In such a situation, blood pressure reduction can cause neurological deterioration (Yatsu and Zavin, 1985). The dilemma is whether or not to lower the blood pressure under such circumstances. The same principles apply as those discussed under the section dealing with stroke.

9) Hypertensive Crisis in Quadriplegic Patients

Hypertensive crises have been reported in patients with transverse lesions of the spinal cord, usually above the origins of the thoracolumbar sympathetic neurons (Naftchi and Tuckman, 1979). Stimulation of dermatomes and muscles supplied by nerves below the injury may evoke

severe hypertension, profound headache, and bradycardia. 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. These critical blood pressure elevations can be prevented by avoiding excessive stimulation of the susceptible portion of dermatomes. Treatment is dictated by the severity of hypertension and the status of target organ function.

10) Hypertensive Crisis Due to Systemic Vasculitis

Abrupt onset of severe hypertension has been known to occur as a complication of necrotizing vasculitis (O'Conell et al, 1985; Travers et al, 1975). The mechanism of hypertension has not been clearly delineated. Possible mechanisms include a direct increase in peripheral vascular resistance as a result of the vasculitis, or via activation of the renin-angiotensin system from renal ischemia.

11) Eclampsia

Eclampsia is a potentially serious cardiovascular complication in a pregnant patient. Although the definitive therapy is delivery of the fetus, the blood pressure should be reduced to prevent neurological cardiac, and renal damage. While other antihypertensive drugs may be effective in reducing the blood pressure, the agent of choice is hydralazine (Silver, 1989), which has a long record of safety. Animal studies have shown that nitroprusside can cause problems in the fetus (Naulty et al, 1981); therefore, its use should be reserved for hypertension refractory to hydralazine or methyldopa. The ganglion blocking drug, trimethaphan should be avoided because of the risk of meconium ileus. In pregnancy induced hypertension, volume depletion may be present and diuretics should be avoided.

12) Post-operative Hypertension

Severe hypertension may occur in some patients in the post-operative period, especially after open heart operations and carotid artery surgery (Estafanous and Tarazi, 1980; Caruthers et al, 1984). The etiology of severe post operative hypertension is multifactorial - withdrawal of antihypertensive drugs, pain, volume overload, and sympathetic activation. Patients with cerebrovascular and coronary artery disease are at a particular danger for post operative hypertension. Therapy should be individualized and in some situations, immediate lowering of the blood pressure is warranted.

13) Severe Hypertension Associated With Burns

Hypertensive crises have been associated with extensive body burns. The mechanisms involved are not fully understood but may involve activation of the renin-angiotensin system (Popp et al, 1981). Prompt control of hypertension is necessary in this instance.

IX. MANAGEMENT

The need to hospitalize the patient, therapeutic options and objectives, and parenteral versus oral therapy depend on the clinical evaluation of the patient. Patients with hypertensive emergencies should be hospitalized and those with hypertensive urgencies may not require admission to the hospital. A therapeutic principle underlying the management of hypertensive crisis is not only to lower the blood pressure quickly but to prevent, arrest, and reverse the target organ dysfunction and damage. Therefore, close supervision of the patient is mandatory while the blood pressure is being lowered. There are no firm guidelines as to the degree of desired blood pressure reduction but a reasonable goal for most hypertensive emergencies is to lower the diastolic blood pressure to 100 (or to reduce the mean arterial pressure by 25 percent) over a period of minutes to hours. Hypertensive emergencies should be preferably managed in an intensive care unit to permit continuous monitoring of the general end hemodynamic status of the patient. An important consideration in treating patients with hypertensive emergencies is the rapidity of onset and duration of action of the chosen drug (Ram and Kaplan, 1984). The physician should be cognizant of the hemodynamic and pharmacological actions of the drug to be used as blood pressure reduction should be accomplished with minimal adverse effects. Next, let's review the drugs useful in the management of hypertensive emergencies and urgencies (Tables 13 and 14).

TABLE 13: PARENTERAL DRUGS USEFUL IN THE IMMEDIATE CONTROL OF SEVERE HYPERTENSION

DRUG	ROUTE AND DOSAGE	ONSET	OFFSET	COMMENTS
NITROPRUSSIDE	IV INFUSION, 0.25 µG/KG/MIN TO 8 µG/KG/MIN	SECONDS	3-5 MIN	THIOCYANATE TOXICITY MAY OCCUR WITH PROLONGED (>48 HRS) OR HIGH-DOSE INFUSION (>15 µG/KG/MIN), PARTICULARLY IN RENAL INSUFFICIENCY
DIAZOXIDE	IV, 50-150 MG Q 5 MIN OR AS INFUSION OF 7.5-30 MG/MIN	1-5 MIN	4-25 HRS	SHOULD NOT BE USED FOR PATIENTS WITH ANGINA PECTORIS, MYOCARDIAL INFARCTION, DISSECTING ANEURYSM
TRIMETHAPHAN	IV INFUSION PUMP, 0.5-5 MG/MIN	1-5 MIN	10 MIN	DRUG OF CHOICE FOR TREATMENT OF AORTIC DISSECTION
LABETALOL	IV, 20 MG Q 10 MIN (CAN INCREASE TO 80 MG DOSES)	5 MIN OR LESS	3-6 HRS	PROMPT RESPONSE; CAN BE FOLLOWED WITH SAME DRUG TAKEN ORALLY
HYDRALAZINE	IM/IV, 10-20 MIN	10-30 MIN	2-4 HRS	MAY PRECIPITATE ANGINA, MYOCARDIAL INFARCTION
NICARDIPINE	IV, 5-15 MG/HR	5-15 MIN	30-40 MIN	MAY CAUSE REFLEX TACHYCARDIA

1) 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 (Figure 10). The hypotensive response occurs within seconds after infusion is started and is dissipated almost as rapidly when the infusion is discontinued (Cohn and Burke, 1979). 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.

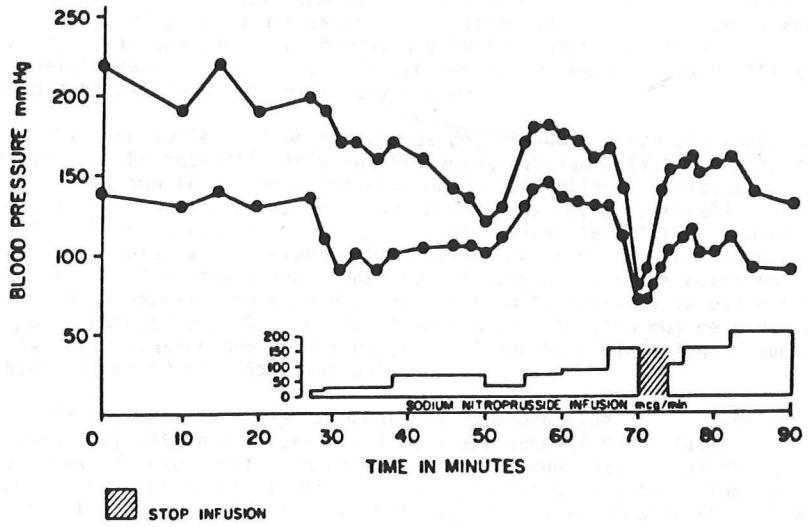


FIGURE 10: BLOOD PRESSURE RESPONSE TO NITROPRUSSIDE INFUSION.

The cardiac output response to nitroprusside is quite variable and depends largely on the pre-existing 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.

Because of its rapid onset of action and potency, nitroprusside infusion must be closely monitored by means of an infusion pump or a microdrip regulator, and intra-arterial blood pressure recording. Last year, the FDA revised the labelling of nitroprusside to underscore the dangers of hypotension and other side-effects (Nightengale, 1991). The initial infusion rate should be no higher than 0.3 micrograms/kg/minute, and this can be increased every five minutes until the desired blood pressure level is obtained. 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. Parenteral treatment of hypertensive crisis generally is needed only for 12 to 48 hours and the drug should be discontinued as soon as alternate modes of therapy have proven effective. Because of its short duration of action, the effects of stopping the therapy will be seen within a few minutes. If indicated, treatment can be resumed promptly. Hypotension is the most common but an avoidable side-effect of nitroprusside therapy.

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

Cyanide toxicity from nitroprusside, although extremely rare, has occurred. Prophylactic infusion of hydroxocobalamin (Vit B_{12a}) 25 mg/hr, has been shown to decrease the cyanide concentration and tissue hypoxia resulting from nitroprusside infusion during surgery (Cottrell et al, 1978). Hydroxocobalamin has one cyanide radical less than cyanocobalamin and, therefore, allows cyanide to combine and form cyanocobalamin which is then excreted in the urine. When cyanide toxicity is suspected on the basis of hypoxemia and metabolic acidosis, nitroprusside infusion should be discontinued and 3% solution of sodium nitrite (4-6 mg) be given by slow I.V. infusion over 2-4 minutes, followed by an infusion of sodium thiosulfate (50 Ml, 25% solution).

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 levels greater than 20 mg/dl are dangerous. Therefore, during high dose infusions of nitroprusside - and especially when renal function is impaired - periodic determinations of plasma thiocyanate levels are recommended; treatment should be interrupted when the thiocyanate level is close to 10 mg/dl. Monitoring of plasma thiocyanate levels is not mandatory as long as the patient's clinical status is closely assessed. Treatment of thiocyanate toxicity demands discontinuation of the drug and institution of dialysis.

It has been suggested that nitroprusside may enhance myocardial ischemia by preferentially dilating the coronary vessels in the non-ischemic myocardium - an effect known as "coronary steal." In a

comparative study, nitroprusside and nitroglycerin produced similar hemodynamic effects but the former increased the ST segment elevations (Chariello et al, 1976). In patients with coronary artery disease, nitroprusside, in contrast to nitroglycerin, was shown to increase ischemic injury via effecting the redistribution of blood flow away from ischemic zones (Mann et al, 1978). Contrasting the above findings is the observation that nitroprusside improves myocardial perfusion in experimental coronary obstruction (Gopal et al, 1983). What are the clinical implications of these findings? Clinicians using nitroprusside must be aware that it has the potential to worsen myocardial ischemia in susceptible patients.

Animal studies have demonstrated that high doses of nitroprusside may reduce the cerebral blood flow (Candia et al, 1978). A similar effect was seen in humans (Brown et al, 1977). We are not for sure about the clinical implications of these observations; in spite of these data, nitroprusside is still recommended for management of hypertensive crises associated with cerebrovascular accidents (Biller et al, 1988; Broft et al, 1989) and cerebral aneurysms (Henriksen et al, 1983).

2) Intravenous Labetalol

Labetalol is a combined alpha- and ß-adrenergic blocking drug that can be used parenterally or orally for the treatment of hypertensive emergencies. Intravenous labetalol administered either as a continuous infusion or bolus injections reduces the blood pressure promptly due to its rapid onset of action (Papademetriou et al, 1982; Wilson et al, 1983; Cressman and Gifford, 1984; Lebel et al, 1985; Huey et al, 1988). Controlled smooth reduction in blood pressure may be obtained by continuous infusion of labetalol at the rate of 0.5 to 2 mg/minute. As with nitroprusside, close monitoring of the patient is required during the infusion of labetalol therapy. Rapid (but not abrupt) lowering of blood pressure can also be accomplished with bolus injections of labetalol (Vidt, 1985; Wilson and Wallin, 1983). Bolus injections of 20 to 40 mg can be given every 10 to 15 minutes until the desired blood pressure level is obtained or until a cumulative labetalol dose of 300 mg is reached. Minibolus injections are safer than the large bolus injections. Labetalol should not be used in patients who may have contraindications to the use of ß-blockers such as heart failure, A-V block, asthma, COPD, etc. Adverse effects reported with labetalol include nausea, vomiting flushing, and headaches.

3) Nicardipine Infusion

Nicardipine is a dihydropyridine calcium antagonist which has been shown to exert a prompt hypotensive effect when given intravenously in patients with severe hypertension (Ram et al, 1989; Tjoa and Ram, 1990; Cook et al, 1990; Clifton et al, 1989). Unlike nifedipine, nicardipine is a water soluble compound suitable for I.V. use. Nicardipine infusion exerts a prompt hypotensive effect. The initial dose of nicardipine infusion is 5.0 mg/hour which can be titrated up gradually to obtain the desired therapeutic effect. Once a stable blood pressure level is

nicardipine pharmacodynamics resemble those of nitroprusside in terms of the onset, duration, and offset of action. Due to its mechanism of action (calcium channel blockade), nicardipine may be beneficial in preserving tissue perfusion. This property may be particularly advantageous in patients with ischemic disorders, e.g., coronary, cerebrovascular, and peripheral vascular disease. From our clinical experience with the use of nicardipine (Ram 1991; Wallin et al, 1989) (Figures 11 and 12), we believe that it may turn out to be a useful therapeutic option in the management of severe hypertension with or without target organ damage. This mode of therapy is particularly attractive since the patients can very easily switched to the oral formulation of the drug. I.V. form of nicardipine has been approved by the FDA very recently and may be available for clinical use in the next few months.

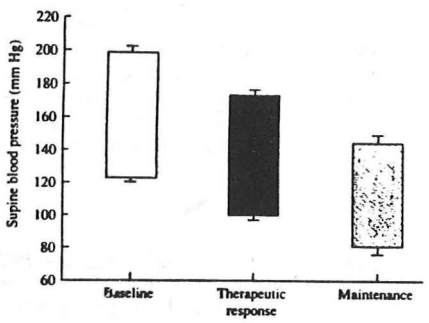


FIGURE 11: ANTIHYPERTENSIVE RESPONSES TO THE INFUSION OF NICARDIPNE IN PATIENTS WITH SEVERE HYPERTENSION. [FROM RAM ET AL, 1989].

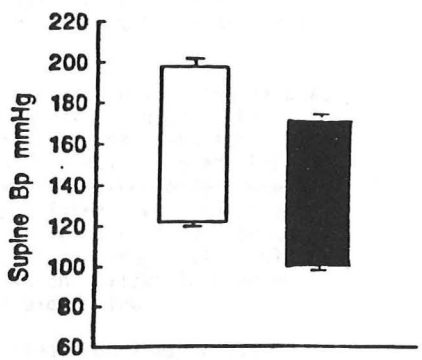


FIGURE 12: PROMPT RESPONSE TO NICARDIPINE INFUSION IN PATIENTS WITH SEVERE HYPERTENSION. [FROM RAM, 1991].

4) Trimethaphan

Trimethaphan camsylate is a ganglion blocking agent. The hypotensive effect of trimethaphan is accompanied by a reduction in left ventricular ejection rate and cardiac output. These attributes make it a drug of choice for the medical treatment of acute aortic dissection. 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. Trimethaphan has a rapid onset of action and its effects dissipate within a few minutes of discontinuation of the drug. The head of the bed should be elevated to augment the antihypertensive effect of this agent. Like nitroprusside, trimethaphan should be administered as a continuous intravenous drip, and constant monitoring is necessary, preferably in the intensive care unit. The usual starting dose of the drug should be 1 mg/min titrated to obtain the desired blood pressure level. After prolonged infusion, tachyphylaxis may result from intravascular volume expansion, which can be partially overcome by effective diuretic therapy.

The major disadvantage of trimethaphan is that it causes parasympathetic inhibition resulting in paralytic ileus, urinary retention, and mydriasis. These effects are particularly likely to occur when the drug is administered for more than a day or two. It is also recommended that the 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.

5) Diazoxide

Diazoxide 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 has no direct effect on the myocardium, but reflex increases in the cardiac output and heart rate may pose a problem to patients with intrinsic cardiac disease. Expansion of plasma volume and edema formation occur during diazoxide therapy, partly because of its direct tubular anti-natriuretic action.

Diazoxide produces a rapid fall in blood pressure within one minute, and the maximum effect is achieved within two to five minutes. The hypotensive effect of a single injection of diazoxide may last for 3 to 15 hours, but if there is no effect from the first injection, an additional dose can be given within 30 minutes. The previously recommended dose of diazoxide was 300 mg or 5 mg/kg given as a rapid intravenous injection. To be maximally effective, the dose should be injected rapidly - between 10 to 30 seconds - to overcome protein-binding of the drug. It should be kept in mind that the sudden depressor effect which follows intravenous bolus injection may be deleterious to cerebral blood flow.

Rapid injection of this relatively large single dose may cause hypotension with resultant myocardial and cerebral ischemia. Smaller bolus injections (Ram and Kaplan, 1979) (Figure 13) and slow intravenous infusions of diazoxide (Garrett and Kaplan, 1982) for the treatment of severe hypertension have been used hoping to reduce the dangers of drastic and precipitous reduction in blood pressure.

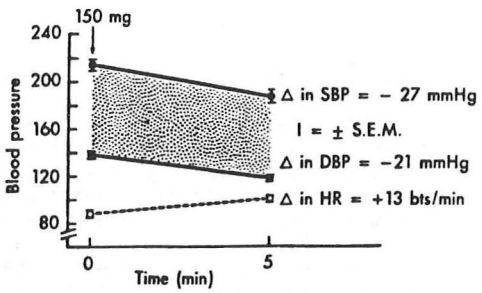


Figure 13: Response to injection of diazoxide, 150 mg. [From Ram and Kaplan, 1979].

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. The excessive hypotensive effect of diazoxide is particularly likely in patients who have had prior antihypertensive therapy. To counteract fluid retention, 40 or 80 mg of furosemide must be given intravenously. The need to use diazoxide has been nearly eliminated by the availability of safe alternative drugs.

6) Hydralazine

The hypotensive action of hydralazine results from a direct relaxation of the vascular smooth muscle and is accompanied by reflex increases in stroke volume and heart rate which can precipitate myocardial ischemia. 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 its duration of action ranges from 3 to 9 hours. The dose and 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 continues to be successfully employed in the treatment of eclampsia.

7) Phentolamine

Phentolamine, an alpha receptor blocking agent, is specifically indicated for treating hypertensive crises associated with increased circulating catecholamines, e.g., pheochromocytoma crisis, certain cases of clonidine withdrawal syndrome, and crises resulting from MAO inhibitor and drug-food interaction. The hypotensive effect of a single intravenous bolus injection is short-lived and lasts less than 15 minutes.

8) Nitroglycerin

The dominant effect of nitroglycerin is venodilation, resulting in reduction of venous return (preload) to the heart. It is a weak systemic arterial dilator with a greater effect on large arteries than on smaller arteries. Low doses cause venodilation; much higher doses are required to produce a fall in systemic blood pressure (Herling, 1984; Hill et al, 1981). Because of its pharmacological actions, nitroglycerin infusion may be particularly beneficial in patients with coronary artery disease with or without hypertension. Although there are no controlled studies, nitroglycerin therapy can be considered in the management of severe hypertension associated with coronary artery disease. The usual initial dosage of nitroglycerin is 5 to 15 micrograms/min and titrated upwards to a desired therapeutic endpoint. It has a rapid onset (within 2 to 5 minutes) and offset of action. Although nitroglycerin has been utilized to achieve controlled hypotension (Fahmy, 1978; Nurenberg, 1991), its main use continues to be in patients with unstable angina and acute myocardial infarction.

9) Fenoldopam

Fenoldopam is an experimental vasodilator that acts by activating dopamine-1 (DA_1) reflectors in the vascular bed. Although its effects are potent on the renal vasculature, resistance in other vascular beds is also reduced. Fenoldopam infusion has been shown to be effective in the immediate management of severe hypertension (Elliott et al, 1990; Reisin et al, 1990). It may cause significant tachycardia. The advantages of fenoldopam, if any, remain to be determined and further investigations are currently in progress.

10) Transition From Parenteral to Oral Therapy

After the immediate management of a hypertensive emergency or urgency with parenteral therapy, oral agents should be initiated at the earliest opportunity. Generally, oral therapy can be begun while tapering off the parenteral drug. If possible, oral drugs should be started with a low dose which can be increased gradually depending on the clinical response. It is important to detect and prevent postural hypotension during transition to oral therapy.

11) Role of Concomitant Diuretic Therapy

Diuretics per se have a limited role in the management of hypertensive emergencies. However, they potentiate the therapeutic response to non-diuretic agents. When the blood pressure does not respond satisfactorily to an adequate dose of the primary agent, adding a diuretic (furosemide) may be helpful. Certainly in volume overloaded states such as heart failure, concomitant administration of a loop-diuretic is indicated for optimal results. Diuretics should not be used routinely in the management of hypertensive crises as prior volume depletion may be present in some conditions such as malignant hypertension. The need for diuretic therapy, therefore, should be individualized on the basis of the

hemodynamic and renal function status of the patient.

X. IMMEDIATE MANAGEMENT OF SEVERE HYPERTENSION WITH ORALLY EFFECTIVE DRUGS

Clinical experience has suggested that antihypertensive drugs given orally either as single or multiple doses lower the blood pressure immediately in patients with severe hypertension (Table 14). Oral administration of a variety of antihypertensive drugs has been utilized in patients with or without concomitant target organ damage. Obviously, this approach is most suitable for patients with hypertensive urgencies, not emergencies.

TABLE 14: ACUTE ORAL THERAPY FOR THE IMMEDIATE CONTROL OF SEVERE HYPERTENSION

DRUG	ROUTE AND DOSAGE	ONSET	OFFSET	COMMENT
NIFEDIPINE	10-20 MG PO OR SUBLINGUAL	5-15 MIN	3-5 HRS	GENERALLY GOOD RESPONSE; SHORT DURATION OF ACTION FOR OPTIMAL DOSAGE NOT STANDARD
CLONIDINE	0.2 MG PO INITIALLY, THEN 0.1 MG/HR, UP TO 0.8 MG TOTAL	0.5-2 HRS	6-8 HRS	PROMINENT SEDATION
CAPTOPRIL	6.5-25 MG PO	15 MIN	4-6 HRS	GENERALLY GOOD, SOMETIMES EXCESSIVE RESPONSE
MINOXIDIL	5-10 MG PO	30-60 MIN	12-16 HRS	TACHYCARDIA, FLUID RETENTION

1) Nifedipine

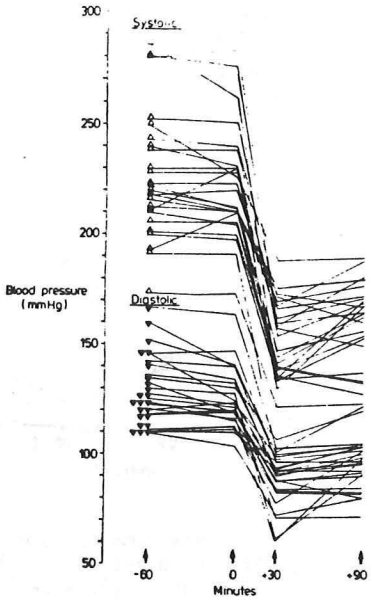
Nifedipine, a calcium channel blocker, given orally, or sublingually has been shown to reduce the blood pressure rapidly and has been found to be useful in the management of hypertensive crisis (Beer et al, 1981; Bertel et al, 1983; Dias et al 1985; Haft, 1985; Davidson et al, 1985; Ellrodt et al, 1985) (Table 15; Figure 14). Immediate reduction in the blood pressure can be accomplished with sublingual (punctured capsule, or nifedipine liquid drawn out of the capsule with a syringe) or oral administration of the capsules. The drug is also effective when the capsule is bitten and then swallowed. The advantages of nifedipine are rapid onset of action and lack of CNS depression. It may cause reflex tachycardia. In fact, both heart rate and cardiac output do increase yet systemic vascular resistance as well as left ventricular end diastolic pressure decrease. Since the duration of action of nifedipine is short, patients who receive this drug for hypertensive emergencies should be monitored for several hours to consider re-administration of the drug. Nifedipine is a useful choice for the management of hypertensive urgencies. In contrast to clonidine therapy, nifedipine has been shown to preserve or increase cerebral blood flow (Bertel et al, 1983). The hypotensive effects of sublingual nifedipine are manifested within 10

minutes and the nadir is seen at about 30 minutes.

Table 15: Nifedipine for Rapid Control of Severe Hypertension - Selected Studies.

	10 mg SL	
17/17	172/109 ⟶	140/88 mm Hg
	20 mg SL	
26/26	204/128 ⟶	160/97 mm Hg
	HR ↑ 13 min^{-1}	
Beer: Chest 1981; 79:571-574		
	10 + 20 mg	
25/25	221/126 ⟶	152/89 mmHg
	HR ↑ 10 min^{-1}	
Bertel: BMJ 1983; 286:19-21		
21/21	181/136 ⟶	132/98 mmHg
	Children	
	0.25-0.5 mg/kg	
Dilmen: AJDC 1983; 137:1162-1165		

Figure 14: Effect of 10-20 mg nifedipine by mouth in hypertensive emergencies (n=25). [From Bertel et al, 1983].



Although the sublingual route has been widely used, nifedipine capsules swallowed intact produce similar antihypertensive effects. From a pharmacokinetic view, different modes of administration result in adequate blood levels of the drug (Love et al, 1985; McAllister, 1986) (Figure 15). In fact, in one study, sublingual nifedipine produced negligible blood levels in contrast to the oral mode of administration (Harten et al, 1987) (Figure 16). Nifedipine (liquid from the capsule) has also been shown to be effective when administered via unusual routes - rectal (Kurosawa et al, 1987; Kleinbloesem et al, 1984) and intranasal (Lopez-Herce et al, 1988). Abrupt fall in the blood pressure induced by nifedipine administration can cause certain adverse effects - symptomatic hypotension, tachycardia, and ischemic events (Wachter, 1987; O'Mailia et al, 1987; Zangerle and Wolford, 1985). Therefore, the clinical need to use nifedipine capsules to lower the blood pressure urgently should be carefully assessed.

Figure 15: Peak nifedipine concentrations in plasma. The mean values for the three routes of administration differ significantly. [From McAllister, 1986].

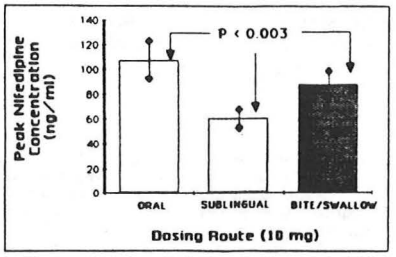
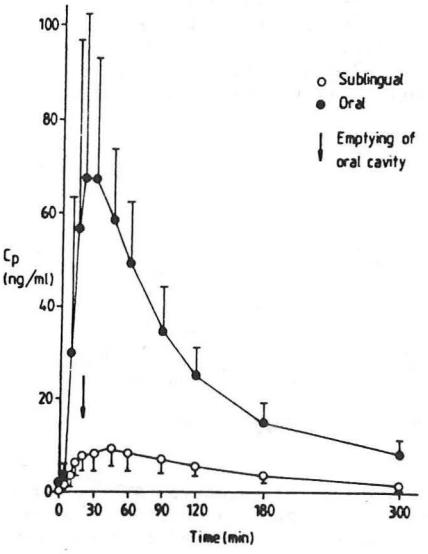


Figure 16: Mean (SD) plasma concentrations (C_p) after administration of 10 mg nifedipine. [From Harten et al, 1987].



2) Clonidine

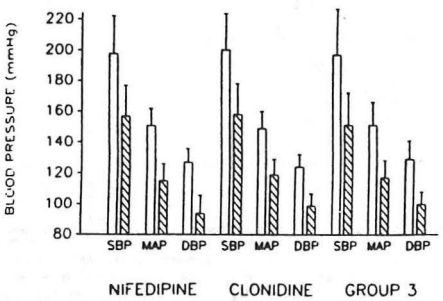
Clonidine therapy has been shown to produce an immediate antihypertensive effect with repetitive dosing (Anderson et al, 1981; Spitalewitz et al, 1983; Cohen et al, 1978) (Table 16). Typically,

Table 16: Selected Studies - Clonidine Therapy for Rapid Control of Severe Hypertension

12/15	195/114 ⟶	143/92 mm Hg
	HR 80 ⟶	51 min^{-1}
	Maximum	0.5 mg
Cohen: CPT 1978; 24:11-15		
34/36	212/139 ⟶	151/103 mm Hg
	Maximum	0.7 mg
Anderson: JAMA 1981; 246:848-850		
20/20	212/134 ⟶	151/104 mm Hg
	Maximum	0.8 mg
Spitalewitz: Chest 1983; 83:404-407		

clonidine loading is accomplished in the emergency room by administering clonidine orally 0.1 mg every hour until the desired goal was obtained. After the availability of nifedipine, clonidine loading has been used infrequently and is on decline. Both clonidine and nifedipine are equally effective in the treatment of hypertensive urgencies (Jaker et al, 1989). Unlike clonidine, nifedipine does not cause sedation. An immediate hypotensive effect can not only be expected from clonidine or nifedipine but also from other drugs such as ß-blockers (Just et al, 1991) (Figure 17).

Figure 17: Pretreatment and posttreatment blood pressures for nifedipine, clonidine, and group 3. Open bars are the blood pressures prior to receiving drug therapy and the slashed bars are the blood pressures at the completion of drug therapy. The vertical lines represent standard deviation. [From Just et al, 1991].



Zeller, et al evaluated the blood pressure responses to 1) clonidine loading (given hourly); 2) initial dose of clonidine followed by placebo given hourly; and 3) maintenance therapy without loading. There was no difference in the therapeutic response to clonidine given hourly compared to a single dose. At 24 hours and at 1 week, there were no differences in control of blood pressure between the groups (Tables 17, and 18)

TABLE 17: SITTING MEAN ARTERIAL PRESSURES AT PRESENTATION AND AFTER LOADING*

Group	Initial BP, mm Hg	BP After Loading mm Hg	ΔBP, mm Hg
1 (N=21)	148.7±2.4	110.1±1.9	-38.6±2.8
2 (N=16)	143.5±2.0	112.5±3.2	-31.1±2.4†

*Mean arterial pressures ([systolic BP + 2 diastolic BP]/3) at presentation and 5 hours after initiation of therapy, as well as mean reduction in mean arterial pressure over the 5-hour interval in group 1 and group 2 patients. Values are expressed as mean ± SEM. BP indicates blood pressure; Δ BP, reduction in BP.
†$p < .05$ vs group 1.

From Zeller et al: Arch Intern Med 1989;149:2186.

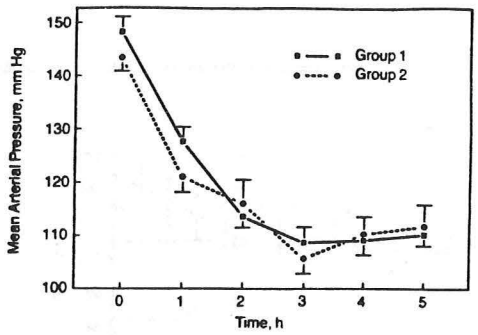
TABLE 18: SITTING MEAN ARTERIAL PRESSURES IN PATIENTS COMPLETING 1 WEEK OF FOLLOW-UP*

	Group 1 (N=15)	Group 2 (N=12)	Group 3 (N=17)
Initial BP, mm Hg	152.4±2.6	142.1±2.2	141.2±2.6
BP at 24 h, mm Hg	113.6±3.7	109.8±3.6	108.7±2.8
BP at 48-72 h, mm Hg	110.1±3.6	103.5±3.3	106.0±2.7
BP at 1 wk, mm Hg	109.3±1.5	102.7±3.8	104.6±3.3
Δ BP at 1 wk, mm Hg	-43.2±2.7 (-49.0 to -37.3)	-40.2±3.0 (-46.8 to -33.6)	-36.7±3.7 (-44.5 to -28.8)

BP indicates blood pressure. Δ BP, reduction in BP. Values are expressed as mean ± SEM, with 95% confidence intervals for reduction in mean arterial pressures at 1 week in each group indicated in parentheses. There was no difference in mean arterial pressure reduction over 1 week between any of the treatment groups (P=.689).
[From Zeller et al: Arch Intern Med 1989;149:2186]

(Figure 18). These data suggest that acute oral antihypertensive drug loading to treat severe hypertension offers no advantages. On the contrary, such therapy can cause hemodynamic and other complications such as prominent sedation.

Figure 18: Mean arterial pressures were determined in group 1 and group 2 patients during the initial 5 hours of emergency department therapy. Values are mean ±SEM for each group at the times indicated. A continuing decline in mean arterial pressure for the first 3 hours after a single 0.2-mg oral dose of clonidine hydrochloride was observed in group 2 patients ($p<.05$). There was no difference in the time course of blood pressure reduction between groups. [From Zeller et al, 1989].



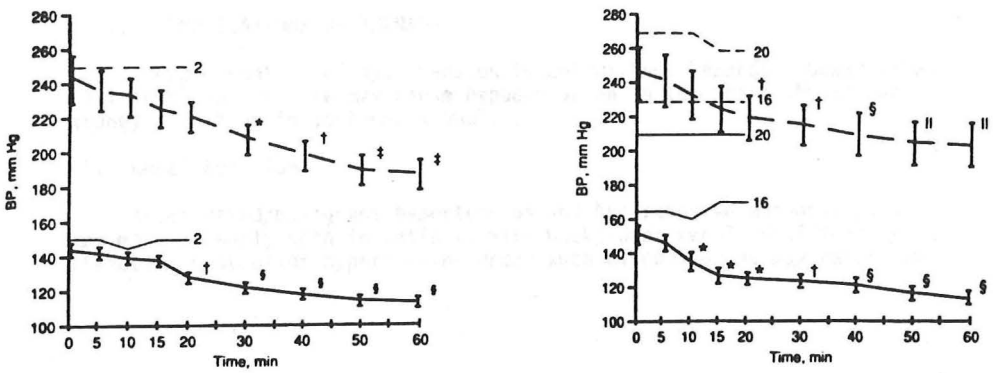
3) Angiotensin Converting Enzyme (ACE) Inhibitors

Table 19: Captopril Therapy for Severe Hypertension - Selected Studies

	25 mg PO
9/9	239/134 ⟶ 204/118 mmHg
	+ Furosemide
	+ 12 Hours ⟶ 140/93 mmHg
Biollaz: EJCP 1983; 25:145–149	

Captopril, an ACE inhibitor, has been found to be effective in the immediate treatment of severe hypertension and hypertensive crises (Biollaz et al, 1983; Sakano et al, 1981) (Table 19). Captopril lowers the blood pressure promptly without causing tachycardia, and thus offers a distinct hemodynamic advantage over direct arteriolar dilators. However, the maximal effect from orally administered captopril may not be attained for as long as two hours. On the other hand, there are some reports documenting the effectiveness of sublingual captopril in the treatment of hypertensive crisis (Tschollar and Belz, 1985; Karachalios and Geogiopoulos, 1989; Haugher-Klevene, 1985). Since experience with sublingual captopril is rather limited, further data have to be generated to define its role in the acute management of hypertensive crisis. High renin states such as malignant hypertension associated with scleroderma renal crisis are particularly responsive to captopril. Enalaprilat, an intravenous converting enzyme inhibitor, has also been found to be effective in the treatment of hypertensive crises (DiPette et al, 1985; Strauss et al, 1986). Volume depleted patients merit closer surveillance as converting enzyme inhibition in this setting may cause profound hypotension and azotemia.

Figure 19: Blood pressure responses to sublingual captopril or sublingual nifedipine administration. [From Angeli et al, 1991).



Comparative studies have demonstrated that captopril and nifedipine are equally effective in immediate treatment of severe hypertension (Angeli et al, 1991; Komsuoglu et al, 1991) (Figure 19). In general, the onset of action of nifedipine is more rapid than that of captopril (by approximately 10 minutes), an insignificant factor in my opinion.

4) Minoxidil

Minoxidil is a powerful direct vasodilator and has been successfully used in the treatment of refractory or severe hypertension. Because of its relatively rapid onset of action and sustained duration, this drug has been used for the treatment of hypertension crises. Minoxidil in doses ranging from 2.5 to 10 mg can be given every 4-6 hours initially in the treatment of severe hypertension. It works best when given along with a diuretic, and an adrenergic blocker is necessary to counteract the reflex tachycardia.

5) Oral Labetalol

Labetalol, a combined alpha- and ß-adrenergic blocker, can be administered orally (100-300 mg) in the treatment of hypertensive urgencies (Zell-Kanter, 1991; Gonzales et al, 1991) (Table 20). Because of its dual adrenergic blockade, the fall in blood pressure is not accompanied by reflex tachycardia, which can be beneficial especially in patients with coronary artery disease.

Table 20: Labetalol Therapy for Severe Hypertension - Selected Studies

15/17	212/136 → 168/95 mmHg HR 90 → 75 min^{-1} Cressman: AHJ 1984; 107:980-985
21/24 No Rx	205/134 → 139/93 mmHg
32/35 Prior	216/134 → 146/94 mmHg Wilson: AJM 1983; Suppl:95-102

XI. COMPLICATIONS OF THERAPY

Rapid control of hypertension is not without hazards. Unwarranted fall in blood pressure may cause hypoperfusion to the heart, brain, or kidney resulting in ischemic sequelae.

1) Renal Function

Accelerated/malignant hypertension and hypertensive encephalopathy are more commonly seen in patients with background renal insufficiency. Effective control of hypertension under such circumstances may result in

transient deterioration of renal function and temporary dialysis may sometimes be necessary (Adelman and Russo, 1981; Barcenas et al, 1976). Long-term treatment of severe hypertension, however, is likely to stabilize or even improve renal function (Mitchell et al, 1980).

2) Cerebral Function and Effects of Acute Antihypertensive Therapy

Normally cerebral blood flow (CBF) is maintained with a safe margin despite wide variations in systemic blood pressure. However, CBF may be disrupted in certain hypertensive crises, e.g., hypertensive encephalopathy, and antihypertensive therapy may adversely influence cerebral circulation. Experimental data obtained from hypertensive rats suggest different antihypertensive drugs may have different effects on cerebral blood flow (Barry et al, 1983; Barry et al, 1984). For example, diazoxide maintains the CBF fairly constant until systemic blood pressure falls to a very low level; hydralazine causes disruption of CBF independent of change in systemic blood pressure; converting enzyme inhibitors and calcium antagonists appear to have a favorable impact on CBF. The relevance of these observations in humans remains to be determined.

3) Other Problems

The complications of antihypertensive therapy usually result from hypotension and sometimes from the nature of therapy - such as diazoxide causing cardiac ischemia and nitroprusside causing thiocyanate toxicity. Sometimes worsening of neurological status following acute reduction in blood pressure (Taylor et al, 1981; Graham, 1975; Singh and Bedi, 1984). These complications can be avoided by careful evaluation of the patient and by choosing an appropriate antihypertensive agent. In this respect, drugs with a short duration of action offer an advantage because unwanted hypotension can be quickly reversed by adjusting the dose or stopping the drug.

In patients recovering from acute cerebrovascular accident or hypertensive encephalopathy, centrally-acting agents such as methyldopa or clonidine should not be used because of their sedative effects. One common error in managing hypertensive crises is to introduce oral drugs prematurely. Another error is the failure to monitor the standing blood pressure in a patient who has been receiving potent antihypertensive agents in the supine position.

XII. CONCLUSIONS

The most critical decision in the management of hypertensive emergencies is to assess the patient's clinical state and to ascertain whether the patient's condition truly needs emergency management. A patient with a real hypertensive crisis should be ideally treated in an intensive care unit. The choice of oral versus parenteral drug depends on the urgency of the situation, as well as the patient's general condition. The level to which the blood pressure should be lowered varies with the type of hypertensive crisis and should be individualized. The choice of

parenteral drug is dictated by the clinical manifestations and concomitant medical problems associated with hypertensive crisis (Table 21). There is no predestined level for the goal of therapy. Complications of therapy, mainly hypotension and ischemic brain damage, can occur in patients given multiple potent antihypertensive drugs in large doses without adequate monitoring. Such complications can be minimized by gentle lowering of blood pressure, careful surveillance, and by individualization of therapy. A relatively asymptomatic patient who presents with severe hypertension, i.e., a diastolic blood pressure 130-140 mm Hg, need not be treated with parenteral drugs. These patients should be managed on an individual basis and the usual course would be to intensify or alter the previous antihypertensive therapy. All too often, asymptomatic patients or those without an acute problem are unnecessarily subjected to immediate therapy. Acute alteration of the height of mercury column does little good and may cause harm. A significant immediate change in the patient's blood pressure may be self-gratifying to the physicians but is not indicated for most patients with asymptomatic severe hypertension. Indiscriminate use of therapeutic options such as nifedipine and furosemide should be strongly discouraged.

TABLE 21: PARENTERAL DRUGS IN THE TREATMENT OF SEVERE HYPERTENSION

	NITROPRUSSIDE	LABETALOL	NICARDIPINE
SEVERE HYPERTENSION	YES	YES	YES
CHRONIC HEART FAILURE	YES	NO	YES
AV BLOCK	YES	NO	YES
ASTHMA AND COPD*	YES	NO	YES
RENAL INSUFFICIENCY	NO	?	YES
VASCULAR DISEAE	?	?	YES
CEREBROVASCULAR ACCIDENT	?	YES	YES
AORTIC DISSECTION	?	YES	-
SWITCH TO SAME DRUG ORALLY	NO	YES	YES

*COPD = CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Once the hypertensive crisis has resolved and the patient's condition is stable, we should look into possible factors that might have contributed to the dangerous elevation of blood pressure such as non-adherence to prescribed therapy or the presence and/or progression of a secondary form of hypertension such as a renal artery stenosis. It is crucial to recognize not only what is a hypertensive crisis but also what is not an emergency.

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