AJH 2001; 14:1154–1167

**Review**

# Management of Hypertensive Crises: The Scientific Basis for Treatment Decisions

Jon D. Blumenfeld and John H. Laragh

The spectrum of disorders associated with an elevated blood pressure (BP) encompasses chronic uncomplicated hypertension and the hypertensive crises, including hypertensive urgencies and emergencies. Although these syndromes vary widely in their presentations, clinical courses, and outcomes they share pathophysiologic mechanisms and, consequently, therapeutic responses to specifically targeted antihypertensive drug types. Nevertheless, hypertensive crises are often treated with drugs which, in that setting are either unsafe or are of unsubstantiated efficacy. The purpose of this review is to examine the pathophysiology of commonly encountered hypertensive crises, including stroke, hypertensive encephalopathy, aortic dissection, acute pulmonary edema, and preeclampsia-eclampsia and to provide a rational approach to their treatment based upon relevant pathophysiologic and pharmacologic principles. Measurement of plasma renin activity (PRA) level often provides insight regarding pathophysiology and predicts efficacy of antihypertensive treatments in the individual patient. However, in hypertensive crises, drug therapy is initiated before the PRA level is known. Nevertheless, the renin-angiotensin dependence (R-type) or volume dependence (V-type) of hypertension can often be deduced by the BP response to drugs that interrupt the renin system (R-drugs) or that decrease body volume (V-drugs). Based upon these considerations, a treatment algorithm is provided to guide drug selection in patients presenting with a hypertensive crisis. Am J Hypertens 2001;14:1154–1167 © 2001 American Journal of Hypertension, Ltd.



Hypertensive crises encompass a wide spectrum of clinical situations that have in common an elevated blood pressure (BP) and ongoing or impending target organ damage. Although they occur most commonly in patients with previously untreated or inadequately treated high BP, hypertensive crises are not defined by, nor is their clinical course predicted by the magnitude of BP elevation.[1,2] Furthermore, some widely used treatments (eg, short-acting nifedipine) are unsafe and have not been approved by the Food and Drug Administration for this indication.[3] In addition, little evidence supports the use of nitroprusside, which is sanctioned as first-line treatment by The Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC) and other authorities.[4]

The purpose of this review is to examine the pathophysiology of commonly encountered hypertensive crises and to challenge some widely used, but unsubstantiated, treatment practices. A new approach for the treatment of hypertensive crises is discussed that incorporates these pathophysiologic principles.

## Definitions and Epidemiology of Hypertensive Crises

The JNC characterizes hypertensive crises as emergencies or urgencies.[4] Accordingly, *hypertensive emergencies* are those situations that require immediate BP reduction (not necessarily to the normal range) to prevent or limit target organ damage. Examples include hypertensive encephalopathy, intracranial hemorrhage, unstable angina pectoris, acute myocardial infarction, acute left ventricular failure with pulmonary edema, dissecting aortic aneurysm, and preeclampsia-eclampsia. *Hypertensive urgencies* are those situations in which it is desirable to reduce BP within a few hours. Examples include upper levels of stage 3 hypertension, papilledema, progressive target organ complications, and severe perioperative hypertension.

Based on these JNC definitions, Zampaglione et al[5] found that hypertensive crises accounted for more than 25% of all patient visits to a medical section of an emergency department, with hypertensive emergencies accounting for one-third of these cases. Although the BP level is not considered a criterion for the diagnosis of a

Received August 17, 2001. Accepted August 17, 2001.

From the The Rogosin Institute and The Department of Cardiothoracic Surgery, New York Presbyterian Hospital, Weill Medical College of Cornell University, New York, New York.

Address correspondence and reprint requests to Dr. Jon D. Blumenfeld, The Rogosin Institute, 505 East 70th Street, New York, NY 10021.

0895-7061/01/$20.00
PII S0895-7061(01)02245-2

hypertensive emergency, all patients in that study had diastolic BP exceeding 120 mm Hg. Central nervous system complications were most prevalent, including cerebral infarction (24.5%), encephalopathy (16.3%), and intracerebral or subarachnoid hemorrhage (4.5%), followed by cardiovascular (acute heart failure and pulmonary edema [36.8%], acute myocardial infarction or unstable angina [12%], aortic dissection [2%]), and eclampsia (4.5%). Altogether, these findings indicate that hypertensive crises are relatively common events that require rational diagnostic and therapeutic strategies.

## Pathogenesis

Blood pressure is the product of the cardiac output (CO) and peripheral vascular resistance (TPR):

(Equation 1)

$$BP = CO \times TPR$$
$$= (\text{heart rate} \times \text{stroke volume}) \times \text{vasoconstriction}$$

For any increase in BP to occur, an imbalance in this relationship is required. Thus, either a disproportionate increase in intravascular volume or peripheral vascular resistance, or both factors, must be present, reflecting a disruption of the normal pressure natriuresis relationship. These fundamental principles apply equally to uncomplicated chronic hypertensions and to the hypertensive crises.[6–8]

Under normal circumstances, the renin-angiotensin-aldosterone system plays a central role in the regulation of normal BP homeostasis.[9] Overproduction of renin by the kidney stimulates the formation of angiotensin II, a potent vasoconstrictor. Consequently, both peripheral vascular resistance and BP increase. These events operate in many patients with chronic uncomplicated essential hypertension. Moreover, in the hypertensive crises, amplification of renin system activity occurs, leading to vascular injury, tissue ischemia, and further overproduction of renin-angiotensin. This vicious cycle contributes to the pathogenesis of hypertensive crises. The pathophysiologic link between the renin system and hypertensive crises has been established by demonstrating that this process can be arrested when the renin-angiotensin system is interrupted either pharmacologically (ie, angiotensin converting enzyme [ACE] inhibitor, $\beta$-blocker, or type 1 angiotensin receptor antagonist) or by removal of an ischemic kidney.[9–11] Other factors induced by excess renin-angiotensin include proinflammatory cytokines and vascular cell adhesion molecules, which may contribute to the vascular sequelae and target organ damage.[12]

The commonly encountered hypertensive crises can be stratified according to these pathophysiologic considerations (Table 1). At one end of the spectrum are disorders in which renin-angiotensin plays a central role in pathogenesis. These disorders are characterized by plasma renin levels (PRA) progressively $\geq$0.65 ng/mL/h and are designated as renin-angiotensin or R type hypertension.[13] Accordingly, they are correctable by agents that suppress plasma renin and hence angiotensin II levels (ie, $\beta$-adrenergic blockers), that reduce plasma angiotensin II levels (ie, ACE inhibitors) or that block angiotensin II entry to angiotensin II vascular receptors (ie, type 1 angiotensin II receptor blockers).[5] Collectively these are referred to as R drugs. At the other end of the spectrum are sodium volume-dependent forms of hypertension, in which plasma renin-angiotensin is not a factor in pathogenesis. These are disorders in which the PRA level is low ($<$0.65 ng/mL/h), and are designated as volume-dependent or V type hypertension. These V forms of hypertension respond to diuretics, aldosterone antagonists, calcium channel blockers, or $\alpha$-adrenergic receptor blockers, which are accordingly designated as V drugs that do not lower BP in R patients.

This classification of hypertensive patients into V or R subgroups according to their plasma renin levels is useful in the evaluation and treatment of the ambulatory patient with uncomplicated hypertension, but is somewhat more limited when applied to the patient with a hypertensive crisis because the PRA value is not immediately available to guide initial treatment, but can still be helpful when returned 24 h later. For this interim period we devised an algorithm in which the BP response to targeted and rapidly acting antihypertensive drugs serves as a surrogate for renin profiling that can be confirmed when the plasma

**Table 1.** Hypertensive emergencies and urgencies

| |
|---|
| **Disorders with high renin** |
| Malignant hypertension |
| **Other medium to high renin states** |
| Unilateral renovascular hypertension |
| Renal vasculitis (scleroderma, lupus, polyarteritis) |
| Renal trauma |
| Renin secreting tumors |
| Adrenergic crises: pheochromocytoma, cocaine abuse, clonidine or methyl DOPA withdrawal |
| **Probable medium to high renin states: PRA ≥0.65 ng/mL/h** |
| Hypertensive encephalopathy |
| Hypertension with cerebral hemorrhage |
| Hypertension with (impending) stroke |
| Hypertension with pulmonary edema |
| Hypertension with acute myocardial infarction or with unstable angina |
| Dissecting aortic aneurysm |
| Perioperative hypertension |
| **Sodium-volume overload, low renin states: PRA levels suppressed <0.65 ng/mL/h** |
| Acute tubular necrosis |
| Acute glomerulonephritis |
| Urinary tract obstruction |
| Primary aldosteronsim |
| Low renin essential hypertension |
| Preeclampsia/eclampsia (PRA values falls from 6 to 10 range of normal pregnancy, to ~1 ng/mL/h) |

DOPA = 3,4-Dihydroxyphenylalanine; PRA = plasma renin activity.

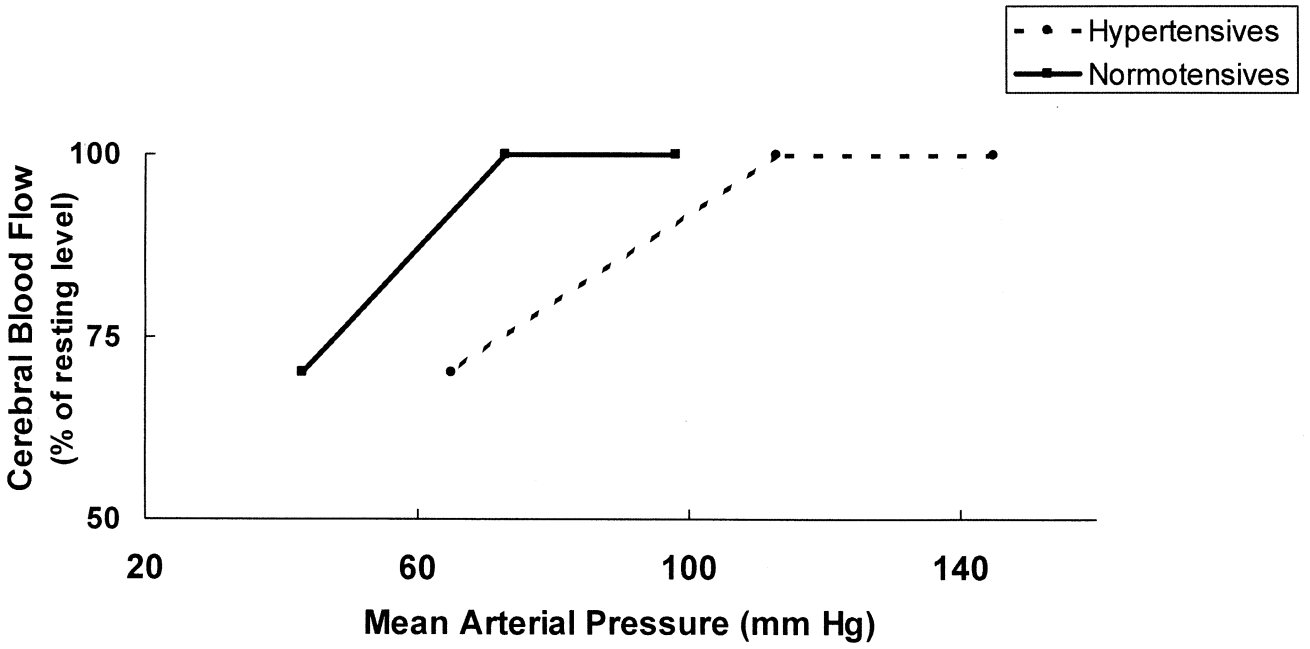


**FIG. 1.** Cerebral autoregulation of blood flow in normotensive subjects and in hypertensive patients. Cerebral blood flow is maintained at a constant level between mean arterial pressure 70 and 90 mm Hg and in hypertensive patients between 110 and 150 mm Hg. Neurologic symptoms occur at higher mean arterial pressure in hypertensive patients.

renin test is returned 24 h later. Thus, the BP response, or lack of a response, to a single drug type administered in single file order provides immediate key information regarding the type (ie, V or R) and the strength of the hypertensive pressor mechanism. This strategy also facilitates the diagnostic evaluation of occult secondary forms of hypertension that are more prevalent in patients with hypertensive crises.[14]

## Disorders Associated With Hypertensive Crises

The traditional strategy for managing hypertensive crises hinges solely on the rapid reduction in BP. This approach often fails to consider the possibly different pathophysiologic mechanisms and, thus, is of limited efficacy and may even be detrimental. The following discussions of the pathophysiology of commonly encountered hypertensive crises focuses on the relevance of these R or V mechanisms for the selection of appropriate R or V antihypertensive drug treatments.[13]

### Stroke

Elevations in arterial pressure occur in more than 80% of patients presenting with acute ischemic stroke.[15] The highest BP levels occur in patients with preexisting hypertension, even when it has been previously treated. However, the appropriate management of hypertension in the immediate period after acute stroke remains controversial. This is underscored by the fact that, in acute ischemic stroke, BP spontaneously declines within 4 days toward prestroke levels without antihypertensive treatment.[15]

**Autoregulation of Cerebral Blood Flow** A brief review of the autoregulation of cerebral hemodynamics provides a basis for understanding the impact of antihypertensive drug treatment on the cerebral circulation during stroke. Autoregulation of cerebral blood flow (CBF) is governed by the relationship between cerebral perfusion pressure (CPP) and cerebrovascular resistance (CVR;

(Equation 2)

$$\text{CBF} = \text{CPP}/\text{CVR} = (\text{mean arterial pressure [MAP]} - \text{venous})/\text{CVR}$$

Cerebral perfusion pressure represents the difference between arterial pressure forcing blood into the cerebral circulation and the venous backpressure. Under conditions of normal CPP, venous pressure is negligible so that CPP is equal to arterial pressure and, consequently, reciprocal changes in CBF and CVR normally occur.

Reductions in CPP may be caused by decrements in systemic arterial pressure or increases in intracranial pressure (ICP), which are transmitted locally to the venous system. Increments in ICP can occur as a consequence of arterial or venoocclusive disease or from an intracerebral hemorrhage. It is evident from Equation 2 that when venous pressure increases abnormally, then a decrease in MAP can markedly reduce CPP and, in turn, diminish CBF.

In normotensive human subjects, changes in CPP that occur over a wide pressure range, from 60 to 150 mm Hg, have little effect on CBF (Fig. 1). [17] Accordingly, increases in CPP promote an increase in vascular resistance, whereas decreases in CPP vasodilate the cerebral vascu-

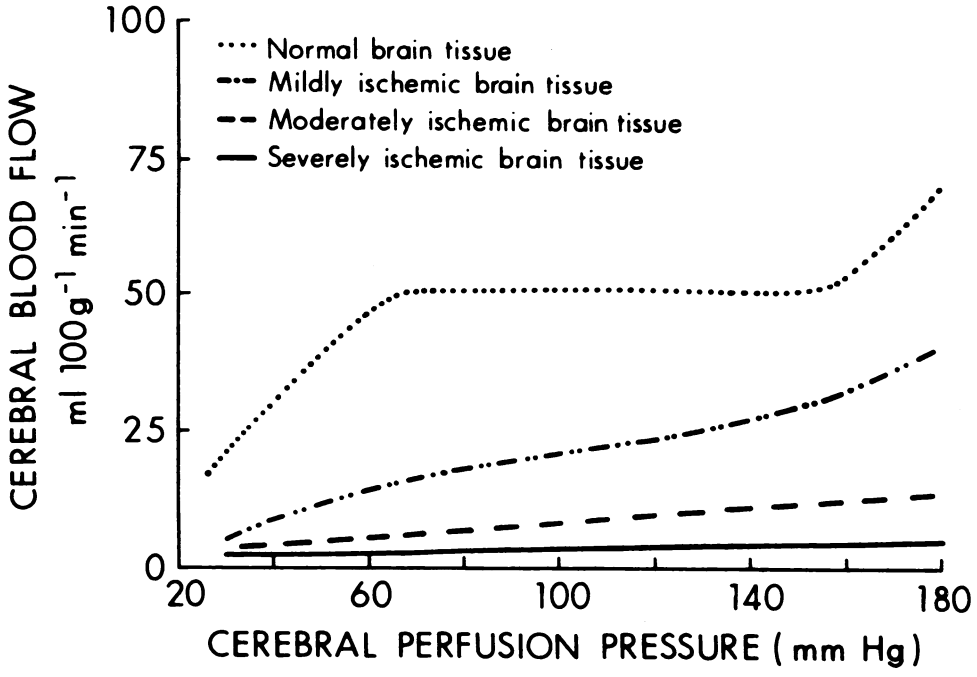


**FIG. 2.** Cerebral autoregulation is impaired during focal ischemia and infarction.[16]

lature. When CPP exceeds the upper limit of autoregulation, CBF increases further and cerebral edema occurs. This "breakthrough" perfusion has been postulated as a mechanism contributing to pathogenesis of hypertensive encephalopathy.[17] Conversely, when CPP decreases below the lower limit of autoregulation, CBF decreases and cerebral ischemia occurs because an insufficient amount of oxygen is extracted by the cerebral tissue.

In patients with uncomplicated chronic hypertension, the relationship between arterial pressure and CBF is altered so that the lower limit of autoregulation is higher than in normotensive subjects (Fig. 1). In untreated hypertensive patients, Strandgaard[17] reported that the lower limit of autoregulation was 113 mm Hg compared with 73 mm Hg in normotensive controls. Thus, the lower limit of autoregulation is about 25% below the resting MAP in both normotensive subjects and patients with uncomplicated essential hypertension.

This observation that the lower limit of autoregulation is about 25% below the resting MAP in patients with uncomplicated hypertension has been interpreted by some authorities to indicate that MAP can safely be lowered to this extent during hypertensive crises associated with acute stroke.[2,4,12,18,19] However, evidence from animal models and stroke patients indicates that cerebral autoregulation is disrupted in ischemic tissue. When an intracerebral artery is occluded, a central core of severe ischemia is surrounded by less ischemic zones where perfusion is maintained by collateral circulation (ie, penumbra).[16,20] Because vessels at the penumbra are maximally dilated, further autoregulation cannot occur and blood flow through these vessels is primarily dependent on cerebral perfusion pressure. When CPP decreases, the autoregulatory curve shifts down and to the right, therefore the CBF is lower at each CPP level. Consequently, when systemic arterial pressure is reduced by substantially <25% below the resting level, viable brain tissue around the ischemic zone is jeopardized (Fig. 2). [16] These observations seriously challenge the widely prescribed recommendation that, during an acute stroke, MAP can be safely reduced by 25% with antihypertensive medication.[2,12,18]

Moreover, randomized controlled clinical trials indicate that antihypertensive drug treatment during an ischemic stroke does not improve clinical outcome and in fact, may worsen it. For example, a large ($n$ = 624), randomized placebo controlled trial of treatment with antihypertensive medication (ie, labetalol, nitroprusside) and recombinant tissue plasminogen activator (rt-PA) during ischemic stroke evaluated the potentially greater risk of intracerebral hemorrhage in hypertensive stroke patients.[21] The study found that in hypertensive patients randomized to receive treatment with rt-PA, antihypertensive treatment after randomization was associated with a fourfold greater risk of death and chronic neurologic impairment when compared with patients who received rt-TPA and who did *not* receive antihypertensive medication after randomization. Furthermore, in patients who were randomized not to receive treatment with rt-PA, antihypertensive therapy after randomization had no benefit in neurologic recovery or death rate. The rt-PA group treated with antihypertensive drugs was more likely to have a more abrupt decrease in BP than those who were not treated with antihypertensive medication. The adverse impact of antihypertensive treatment could not be attributed to other patient characteristics

(eg, age, stroke severity, or severity of hypertension), which were similar in the rt-PA and non-tPA treatment groups. In summary, this important controlled trial highlights that during ischemic stroke: 1) there is no demonstrable benefit of antihypertensive treatment regardless of whether concurrent rt-PA is used and 2) concurrent treatment with rt-PA and antihypertensive medication appears to have a detrimental effect on clinical outcomes, including neurologic recovery and survival.[21]

Other placebo-controlled studies support and extend these observations regarding the adverse effect of antihypertensive treatment during an ischemic stroke. Kaste et al[22] reported that, compared to the placebo group, patients randomized to treatment with nimodipine, a dihydropyridine calcium channel blocker (CCB), had a higher mortality rate during 1-month and 3-month follow-up periods. Although systolic BP was significantly lower in the nimodipine group than the placebo group during the first week of treatment, no association between BP levels and the higher mortality rate was reported.

In a relatively small ($n$ = 16 patients), randomized placebo-controlled trial of the dihydropyridine CCB nicardipine, CBF in the infarcted area either failed to increase, or decreased. In contrast, in those treated with either an ACE inhibitor (captopril) or a central $\alpha_2$-receptor agonist (clonidine), CBF increased significantly in the infarcted region.[23] Patients were randomized to either placebo or active drug treatment within 72 h of onset of symptoms. Blood pressure decreased equivalently in active treatment and placebo groups and clinical outcomes were similar regardless of whether or not drug treatment was used. However, the type of antihypertensive agent used appeared to influence cerebral hemodynamic patterns. These observations suggest again that autoregulation of CBF may be adversely influenced by CCB, but not by an ACE inhibitor or a central sympatholytic agent. Still other studies have also reported that antihypertensive treatments with an ACE inhibitor or $\alpha_1$-adrenoceptor blocker also preserve CBF.[24,25]

## Subarachnoid and Intracerebral Hemorrhage

Hypertension occurs commonly in the early period after intracerebral hemorrhage. It is more severe and, in contrast to the BP elevation during ischemic stroke, is less likely to spontaneously improve during the first few days after presentation.[15,26]

Severe hypertension is a common feature of subarachnoid hemorrhage.[16,27] Nimodipine, a dihydropyridine CCB, significantly improves outcome in patients with subarachnoid hemorrhage. However, transient hypotension is a relatively common side effect of nimodipine, particularly when it is administered intravenously.[28,29] Although the decrease in BP usually responds to hydration, approximately 30% of patients also require treatment with vasoconstrictors (eg, dopamine, phenylephrine, norepinephrine) to reverse its vasodilating effect. These offsetting therapeutic strategies have unpredictable and unsettling consequences, particularly now that surgery for ruptured aneurysms is done in older patients with concomitant coronary artery disease.[28]

Treatment with a dihydropyridine CCB during the early period after intracerebral or subarachnoid hemorrhage has a significant effect on cerebral hemodynamics.[30] Within 30 min after a single dose of short-acting nifedipine, MAP decreases by 20%, mean intracerebral pressure increases by 40%, and consequently, CPP decreases by 40%. Patients with higher pretreatment intracerebral pressures (40 mm Hg) have more marked reductions in CPP. This means that nifedipine promotes cerebral edema, reduction in CPP, and, hence, impairs autoregulation of CBF.[30] However, the long-term clinical impact of these results cannot be interpreted fully because the neurologic outcomes of these patients were not reported.

However, the adverse hemodynamic responses of dihydropyridine CCB may account for their limited therapeutic efficacy reported in some treatment trials. For example, The Cooperative Aneurysm study, a large ($n$ = 906), randomized controlled trial in patients with aneursymal subarachnoid hemorrhage compared high-dose intravenous nicardipine with a control group treated with volume expansion. In that study, hypotension occurred twice as frequently in the nicardipine group (34.5% $v$ 17.5%).[31] Overall, neurologic outcome and survival were similar in these two groups at 3-month follow-up, although the incidence of symptomatic vasospasm was greater in the control group than in the nicardipine group.

In summary, data from controlled studies of antihypertensive drug therapy in acute stroke are limited but useful when considering treatment options. The evidence indicates that in ischemic stroke, BP spontaneously decreases to prestroke levels within a few days.[15] There is no evidence from clinical trials to support the use of antihypertensive treatment during an acute stroke in the absence of other concurrent disorders (eg, aortic dissection or heart failure; see below). Moreover, data from both laboratory and clinical studies strongly suggest that antihypertensive treatment may adversely affect cerebral autoregulation in acute stroke. In particular, dihydropyridine CCB and other direct vasodilators promote changes in cerebral hemodynamics that might be detrimental. Although the favorable effect of nimodipine in patients with acute subarachnoid hemorrhage has been established, at the same time, treatment-induced hypotension may limit its efficacy.[30,31]

## Malignant Hypertension and Hypertensive Encephalopathy

Malignant hypertension is characterized by fibrinoid necrosis in arterioles and myointimal proliferation in small arteries, which is manifested by neuroretinopathy and renal disease.[32] It rarely occurs de novo and is usually a sequel to various forms of benign hypertension as well as

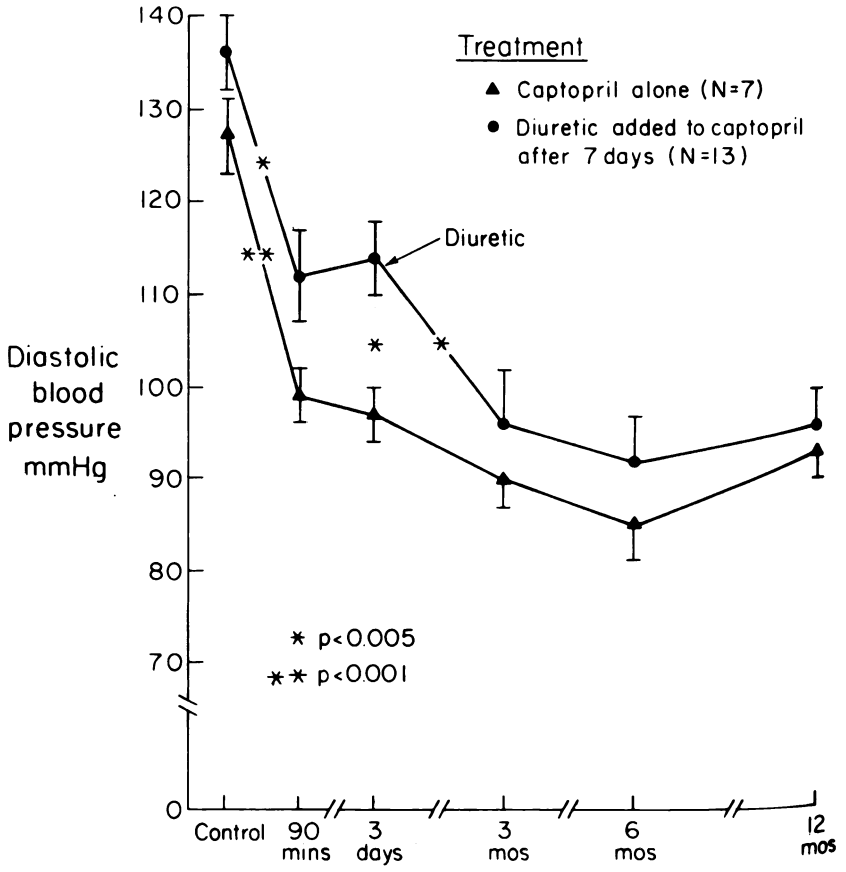


**FIG. 3.** The acute and long-term effects of captopril treatment on diastolic blood pressure in patients with malignant hypertension and malignant encephalopathy. Patients whose diastolic pressures were greater than 105 mm Hg after 7 days of treatment were given supplemental diuretics.[11]

to secondary forms including renovascular hypertension, scleroderma, and vasculitis. Unless treated with antihypertensive medication, the mortality rate in such patients exceeds 90% within 1 year after presentation.

Hypertensive encephalopathy is characterized by generalized signs and symptoms including headache, lethargy, seizures, and papilledema. The mechanism responsible for the generalized neurologic findings has been attributed to rapid elevation of cerebral perfusion pressure beyond the upper limit of autoregulation (see above), leading to cerebral edema and reduced CBF. Focal neurologic findings are not characteristic, although they may develop if cerebral hemorrhage or infarction occurs.[16]

The rapid increase in BP is most commonly due to massive overproduction of renin and angiotensin II in response to renal ischemia.[10] This enhances pressure natriuresis, which further stimulates renin-angiotensin-aldosterone release to thereby enhance renin-related metabolic abnormalities, including hypokalemia and metabolic alkalosis,[10] and also enhance the potential for angiotensin-induced cerebral, cardiac, and renal vasculotoxicity. The central role of excess renin system activity in this process is supported by high PRA levels that occur before treatment, by a marked reactive plasma renin increase during treatment with an ACE inhibitor,[11] or by the marked suppression of renin level levels by propranolol,[33] and by the dramatic clinical improvement within minutes after initiating these antirenin therapies.[11,33,34]

These observations provide a pathophysiologic basis for the treatment of malignant hypertension and hypertensive encephalopathy with antihypertensive agents that target the renin-angiotensin system. For example, captopril, an orally active ACE inhibitor, is safe and effective in both the acute setting and during prolonged treatment (Fig. 3). It is administered orally and the onset of action is 30 to 60 min. Enalaprilat, an intravenously administered, rapidly acting ACE inhibitor, is also effective in this setting.[35] Furthermore, ACE inhibitors and $\beta$-adrenergic blockers,[33] which interrupt the renin-angiotensin system at different sites, each favorably shifts the cerebral autoregulatory curve, therefore CBF is maintained at baseline despite lower arterial pressures (see above).[23,24,36] In contrast, the empiric use of diuretics or direct vasodilators (eg, hydralazine, nitroprusside) may be less effective because they stimulate reactive renin secretion (see below).[9]

## Aortic Dissection

Aortic dissection is classified as type A if it involves the ascending aorta or type B if it does not.[37] This distinction

is based on their differing responses to treatment. In general, type A dissections have a lower mortality rate when treated surgically, whereas type B dissections respond more favorably to medical therapy.[37,38] Despite these differences, the initial medical management of both types of aortic dissection is similar and is designed to prevent its propagation, hemorrhage, and rupture.

The rate of increase of the aortic pulse wave, dP/dt, is the dominant force that determines the risk of aortic dissection and its complications.[39] Factors that contribute to dP/dt include myocardial contractility, BP, and heart rate. Interventions that reduce myocardial contractility and the rate of increase of the pulse wave contour will decrease the energy absorbed by the damaged aorta and, thus, will attenuate these risks. Accordingly, both β-adrenergic and ganglionic blockers are the cornerstone of treatment for aortic dissection.[38]

Hypertension is nearly ubiquitous in patients with aortic aneurysms. Of the more than 400 patients who have undergone surgical repair at New York Presbyterian Hospital, hypertension is present in 98% of those with descending thoracic or thoracoabdominal aneurysms and 89% with ascending aortic aneurysms (Leonard Girardi, MD; personal communication). The lowest tolerated BP is the target for treatment. However, hypertension is a heterogeneous disorder and, therefore, BP does not decrease uniformly in all patients during monotherapy with a β-blocker.[9,33] Therefore, although β-blockade rapidly decreases myocardial contractility and heart rate in all patients, additional antihypertensive agents might be required.

Nitroprusside is widely recommended and commonly used in patients with aortic dissection because it has a rapid onset and brief duration of action and, thus, can theoretically be titrated quickly.[40] However, even when nitroprusside is infused at a low dose, aortic dP/dt increases markedly unless there is concurrent β-blockade.[41] The increase in dP/dt during nitroprusside infusion is the consequence of baroreflex stimulation and related activation of the renin-angiotensin-aldosterone system.[42–44] Peripheral vascular resistance and renal sodium reabsorption are both amplified and, thus, the antihypertensive effect of nitroprusside is attenuated—a phenomenon referred to as nitroprusside resistance.[42]

Dihydropyridine CCBs are commonly used for the treatment of hypertension and have been advocated for use in aortic dissection.[45] However, as with nitroprusside, these agents increase heart rate, and contractility, and plasma catecholamine levels.[46] Therefore, the routine use of dihydropyridine CCB in the absence of β-adrenergic blockade is not justifiable.

## Acute Pulmonary Edema and Congestive Heart Failure

Heart failure is defined as the pathophysiologic state in which the heart is unable to pump blood at a rate commensurate with the body's metabolic requirements. This clinical syndrome is characterized by signs and symptoms of intravascular and interstitial volume overload or by manifestations of inadequate tissue perfusion, such as fatigue or reduced exercise tolerance.[47] In the Framingham population, more than 90% of heart failure patients have a history of hypertension. Moreover, it is one of the characteristic presenting signs and symptoms of ischemic nephropathy, defined as impaired glomerular filtration caused by hemodynamically significant bilateral renal artery stenosis.[48] Accordingly, hypertension can be both the cause and consequence of acute pulmonary edema, reflecting left ventricular systolic and diastolic dysfunction in the setting of excess activation of the renin-angiotensin-aldosterone axis and other neurohormonal systems.

**Renin System Activation in the Pathogenesis of Heart Failure** Compensatory neurohormonal and hemodynamic mechanisms maintain CO and peripheral perfusion when cardiac function is impaired.[49,50] Progressive deterioration in cardiac performance occurs as a consequence of the maladaptive mechanisms. The modern treatment of heart failure is directed toward the correction of these pathophysiologic processes.[51–56]

The renin system plays an important role in the pathogenesis of progressive left enlargement and dysfunction that occur after myocardial infarction (MI). Treatment with captopril, an ACE inhibitor, improves cardiac performance and decreases mortality by about 20% from cardiovascular and other causes.[57] Type 1 angiotensin II receptor blockade appears to be as effective as ACE inhibitors in the treatment of decompensated heart failure.[58,59] Moreover, the significance of aldosterone in the pathogenesis of heart failure is underscored by the striking efficacy of spironolactone, a mineralocorticoid receptor antagonist that by promoting natriuresis and diuresis with potassium retention significantly improves survival.[60,61]

The beneficial effects of ACE inhibitor treatment in heart failure are not limited to patients with very high pretreatment plasma renin levels. Packer and co-workers[51] found that approximately 50% of patients in the low-medium range (PRA $<2$ ng/mL/h) had sustained improvements in left ventricular function and symptoms during captopril treatment. These benefits were accompanied by a 15-fold increase in mean PRA level, reflecting a marked renin response to the blockade of angiotensin II production by the ACE inhibitor. In contrast, captopril was not beneficial in those patients whose renin levels did not increase during treatment. These results suggest that the plasma renin response is heterogeneous in heart failure, just as it is in hypertension, therefore its reactive increases are predictive of the efficacy of ACE inhibitor treatment. Conversely, no reactive increases in renin levels indicate the absence of an operating renin factor, so that the ACE inhibitor is unlikely to be effective.

In summary, decompensated heart failure can be both a cause and consequence of a hypertensive crisis, reflecting

excess activation of the renin-angiotensin-aldosterone system with an increased total body sodium content. Treatment strategies include diuresis, preferably with spironolactone,[60,61] best combined with R drugs that reduce or interrupt renin-angiotensin II release, formation, or its binding to the type 1 receptor (ie, β-adrenergic receptor blockers, ACE inhibitors, or angiotensin II receptor blockers).

## Acute Myocardial Infarction

Acute MI, like congestive heart failure, can occur in the setting of a hypertensive crisis. Excess renin system activation commonly occurs in the earliest stages of an acute heart attack.[62] Recent studies of acute MI have stressed the importance of neurohormonal activation (ie, renin system activation) during acute MI as a predictor of several clinical outcomes, including functional class, ventricular aneurysm formation, ventricular performance, and survival.[49,63] Thus, the pathophysiologic role of the renin-angiotensin system is highlighted by clinical trials of ACE inhibitor treatment during acute MI, encompassing more than 100,000 patients, which consistently demonstrate significant improvement in survival related to administration of these antirenin (R) agents. Moreover, β-adrenergic receptor blockers, which attenuate the activity of both the adrenergic and the renin-angiotensin systems, dramatically improve survival in the post-MI patient and, therefore, remain the cornerstone of treatment.[64,65]

In contrast, there is evidence that direct arterial vasodilators, such as nitroprusside and short-acting dihydropyridine calcium channel antagonists, can be detrimental during an acute MI. A crossover study of nitroprusside and nitroglycerin in patients during an acute transmural MI found that the MAP decreased significantly with both drugs when compared with pretreatment levels.[66] However, unlike nitroglycerin, nitroprusside increased heart rate and provoked ST segment elevation, whereas nitroglycerin decreased ST segments toward normal levels. Studies in experimental models of acute MI found that nitroprusside decreased transmural blood flow and provoked ST segment elevation, whereas nitroglycerin increased transmural blood flow and attenuated the magnitude of ST segment elevation. These data with nitroprusside are consistent with redirection of coronary blood flow away from regions of myocardial ischemia, referred to as coronary steal.[66]

Despite their potent antihypertensive actions, short-acting CCB have been implicated in complications during acute MI and after cardiovascular surgery.[67–70] Hence, these agents are contraindicated for the treatment of hypertensive crises, particularly when associated with cardiovascular disease. In contrast, β-adrenergic blockers and ACE inhibitors improve survival in the setting of acute MI and, therefore, represent the first line of treatment.[57,65]

Cocaine intoxication is associated with uncontrolled hypertension and coronary artery vasoconstriction leading to angina, MI, and sudden cardiac death.[71] The principal effects are stimulated by α-adrenergic-mediated events. Accordingly, selective $\alpha_1$-adrenergic receptor blockade, combined α,β-adrenergic blockade (eg, labetalol), or non-dihydropyridine CCB (eg, verapamil) are effective treatments.[72] In contrast, β-blockade, without concurrent $\alpha_1$-adrenergic receptor blockade may exacerbate these conditions.[72,73]

## Preeclampsia–Eclampsia

This pregnancy-specific syndrome usually occurs after 20 weeks' gestation or earlier in the case of trophoblastic diseases such as hydatidiform mole or hydrops.[74] It is characterized by gestational BP elevation and proteinuria. Gestational BP elevation is defined as a systolic pressure >140 mm Hg or diastolic pressure >90 mm Hg in a woman who was normotensive before 20 weeks' gestation. Proteinuria is defined as ≥300 mg in a 24-h specimen. The pathophysiologic mechanisms underlying preeclampsia are not well established. Blood pressure elevation in this syndrome is characterized by increased responsiveness to angiotensin II and other vasoconstrictor substances, as well as endothelial dysfunction characterized by decreased production of, or responsiveness to endothelium-derived vasodilators.

Preeclampsia is associated with protean clinical and laboratory manifestations including headache, visual disturbance, epigastric pain, serum creatinine >1.2 mg/dL, platelet count <100,000 with concurrent microangiopathic hemolytic anemia and elevated lactate dehydrogenase, and elevated hepatic transaminase activities. Eclampsia is defined as the occurrence of seizures, without an antecedent cause, in a patient with preeclampsia.[74]

The clinical and laboratory manifestations of preeclampsia are reversible and begin to subside after delivery. The timing of delivery is determined by the relative risks and benefits to maternal health and fetal development. These considerations have been summarized elsewhere.[74]

Hospitalization is indicated for onset preeclampsia or severe gestational hypertension. Variable duration of antepartum management with restricted activity can be accomplished for patients between 23 and 32 weeks' gestation. Intravenous magnesium sulfate reduces the frequency of eclampsia among patients with pregnancy-induced hypertension or severe preeclampsia, although its usage in patients with milder manifestations is not well defined.[75] Treatment with specific antihypertensive agents should be initiated when diastolic pressure exceeds 105 mm Hg or when it increases rapidly from a normal range to >100 mm Hg.

The choice of antihypertensive drug is limited by its potential for adversely affecting fetal development. Most notably, ACE inhibitors and angiotensin II receptor antagonists are contraindicated in pregnancy because of the associated increase in fetal and neonatal morbidity and

death.[76] α-Methyldopa is the mainstay of treatment for gestational hypertension because of a low risk of fetal complications.[77] In patients with preeclampsia and severe hypertension (>160/110 mm Hg), there are relatively few antihypertensive medications that are safe and effective for parenteral administration. Hydralazine, which can be administered by intravenous bolus or by intramuscular injection, has a rapid onset of action. Common side effects include reflex tachycardia, hypotension, and fluid retention caused by activation of the renin-angiotensin-aldosterone system. Labetalol is also effective in this setting, either as an intravenous bolus or by continuous infusion. It is contraindicated in patients with asthma or with decompensated heart failure. Nitroprusside can cause profound reflex bradycardia and hypotension during treatment of preeclampsia.[78] The risks and benefits of nitroprusside and short-acting CCB in hypertensive crises have been outlined elsewhere in this discussion. These agents should be used with extreme caution in pregnancy.

## Approach to the Patient With the Hypertensive Crisis

Hypertensive crises share all the pathophysiologic mechanisms and target organ complications (eg, MI, stroke, renal failure) that operate in patients with milder forms of high BP and, thus, together can be viewed as part of the spectrum of human hypertension. Accordingly, BP is reduced, in the hypertensive crises and in the chronic forms of hypertension, by the same specifically targeted drugs that interrupt relevant pathophysiologic mechanisms. In the ambulatory chronic hypertensive patient, treatment is usually accomplished after several office visits, allowing for the confirmation of hypertension and assessment of cardiovascular risk. At New York Presbyterian Hospital, this includes an evaluation of renin system activity, which often provides information regarding pathophysiology and, thereby directs selection of antihypertensive drug treatment and stratification of cardiovascular risk. On the basis of the entry plasma renin level the primary antihypertensive agent is chosen from either the R or V drug class. If the entry PRA is ≥0.65 ng/mL/h, we begin with an antirenin system R drug, either a β-blocker to lower plasma renin levels, an ACE inhibitor to reduce angiotensin II formation, or an angiotensin receptor blocker (ARB) to block the engagement of angiotensin II at its vascular receptor. Conversely, if the PRA is <0.65 ng/mL/h, sodium volume hypertension is likely and the therapy is begun instead with an antisodium volume V drug. These include the aldosterone antagonists (ie, spironolactone), α-blockers, or CCBs. This approach optimizes treatment even for refractory hypertension.[79]

In a hypertensive crisis, this approach is adapted to enable the pace of diagnosis and treatment to accelerate. The decision to promptly lower BP necessarily limits the availability of diagnostic information (eg, PRA, plasma catecholamines) before treatment begins. Nonetheless, the same concepts that are used to direct antihypertensive treatment in the ambulatory patient can be applied to the hypertensive crisis by evaluating the BP responses to one agent from each drug class. Because each drug is selectively targeted to a potential pathophysiologic mechanism, a reduction in BP, or alternatively, the lack of a BP response will provide information regarding the mechanism of hypertension, to thereby indicate what additional diagnostic evaluation is required (see below).

A thorough initial history and physical examination are essential to guide selection of appropriate treatment. Direct questioning regarding the level of compliance with current antihypertensive medications (including prescription, over-the-counter, and recreational drugs) may establish the basis of the hypertensive crisis.[19] A history of comorbid conditions is also central to this assessment. Laboratory tests are obtained that can elucidate the hypertensive mechanism and define the extent of target organ damage. These tests include serum electrolytes, blood urea nitrogen, creatinine, complete blood count, platelet count, electrocardiogram, chest X-ray, and urinalysis. Plasma renin activity and catecholamine levels are also measured, although these results are not available when treatment of the hypertensive crisis is initiated.

Special attention also should be directed to whether there is evidence for aortic dissection. If it is suspected, initial treatment with a $\beta_1$-adrenergic blocker is indicated. Esmolol can be administered as a continuous infusion and is appropriate in the perioperative setting. If surgery is not planned, but a parenteral route of drug treatment required because the patient has an altered mental status or gastrointestinal absorption is impaired, then bolus intravenous doses of metoprolol may be preferable to esmolol because it is simpler to administer. If there is a history of asthma or if bronchospasm is present, then a ganglionic blocker or a non-dihydropyridine CCB can be substituted. If the BP is not controlled during β-blockade, then addition of a drug with a complementary action, such as an α-adrenergic blocker or diuretic is appropriate. If the patient requires emergent surgical repair, then nitroprusside should be infused only after adequate β-blockade is established to blunt the undesirable effects of nitroprusside (or CCB) on aortic dP/dt.

In the absence of an aortic dissection, one agent from each antihypertensive drug class is administered in single file order, first an R drug (captopril or enalapril) to assess the renin factor, then an R + V drug, using the α and β blocker labetolol, to determine the likelihood of catecholamine involvement, and finally a primary V drug (furosemide) to assess the sodium volume involvement, as indicated by the BP responses to each individual drug type (Table 2). The specific order in which the drugs are administered might vary depending on the history, physical examination, and laboratory findings. In addition, for many patients orally active agents can be used. The indications for parenteral route of administration include al-

**Table 2.** Drugs for treatment of hypertensive crises

| Drug Class | Oral Drug | Parenteral Drug |
|---|---|---|
| ACE inhibitor | captopril | enalaprilat |
| $\alpha_1$-adrenergic blocker | terazosin, doxazosin, prazosin | phentolamine |
| Diuretic | furosemide | furosemide |
| $\beta_1$-adrenergic blocker | metoprolol | esmolol metoprolol |
| $\alpha_1,\beta_1$-adrenergic blocker | labetalol carvedilol | labetalol |
| Central $\alpha_2$-agonist | clonidine guanfacine | clonidine (transdermal) |

ACE = angiotensin converting enzyme.

tered mental status, gastrointestinal disorders that limit absorption, and requirement for emergent surgery.

## Treatment Algorithm (Table 2, Fig. 4)

1. An *ACE inhibitor* is given first to assess the presence and degree of a renin (R) factor in causation because of the known vasculotoxic and pressor actions of angiotensin. The full action of an oral dose of captopril or of intravenous enalaprilat is approximately 30 to 60 min. Significant BP reduction is indicative of renin-dependent vasoconstriction, a common feature of malignant hypertension, regardless of whether secondary forms of hypertension are present. However, a favorable BP response warrants further evaluation of potentially curable forms of renin-dependent hypertension. These agents should also be selected first in patients with decompensated heart failure, acute pulmonary edema, or an acute coronary syndrome (eg, acute MI, unstable angina). If the BP does not decrease after the initial dose, then a renin-dependent mechanism is unlikely and an alternative drug class should be evaluated. Angiotensin converting enzyme inhibitors are contraindicated for use in preeclampsia–eclampsia (see above).
2. *$\alpha_1$-Adrenergic receptor blocker.* This drug class is effective in patients with pheochromocytoma and also in patients with low renin forms of hypertension.[80] The onset of action of terazosin, an oral agent, is approximately 1 h. Phentolamine is an intravenous agent in this class that has immediate onset of action. Blood pressure reduction indicates an $\alpha$-adrenergic mechanism of vasoconstriction and directs the diagnostic evaluation toward pheochromocytoma. Lack of a BP response directs treatment toward an alternate drug.
3. *Diuretic.* Patients with sodium-sensitive, volume-dependent forms of hypertension will have a reduction in BP during treatment with a diuretic. This drug class should be used earlier in the algorithm in patients presenting with decompensated heart failure, renal failure, or edema. Loop diuretics are effective within 30 to 60 min. Escalating doses should be used until a diuresis occurs. Dialysis and ultrafiltration are required for azotemic patients who are unresponsive to diuretic therapy.
4. *Central $\alpha_2$-receptor agonist.* Abrupt cessation of clonidine, guanfacine, or $\alpha$-methyldopa can cause a withdrawal syndrome characterized by restlessness, severe headache, excess salivation, nausea, insomnia, and stomach pain associated with marked escalations in BP and heart rate. These signs and symptoms are similar to pheochromocytoma and can be alleviated by reinstitution of the withdrawn drug or by combined $\alpha$- and $\beta$-adrenergic receptor blockade. When a history of treatment with this drug class is elicited, then restoration of the agent should be the first in the treatment algorithm. If parenteral treatment is required, then infusions of labetalol or both phentolamine and esmolol are also appropriate. In addition, transdermal clonidine, which requires several hours to reach a therapeutic level, can be applied. However, for the longer term, alternate treatments should be sought in the patient who may not be compliant to this drug class.
5. *Combined $\alpha_1$-, nonselective $\beta$-adrenergic receptor blockade.* Labetalol is effective in the treatment of a hypertensive crisis. It can be administered either orally or parenterally as frequent, intravenous boluses or preferably as a continuous infusion. Oral therapy with 200 mg, in hourly doses up to 1200 mg reportedly controlled BP in an emergency department setting.[81]
6. *Nitroprusside* is frequently recommended as the first line treatment for hypertensive crises because of its rapid onset of action and ease of BP titration.[4,12,18] However, several of the following factors limit its use:

   a. It is common for BP to be unintentionally reduced below a safe target level during treatment.[42] This may occur because the patient is volume depleted, has a vasodepressor reflex response (Bezholdt-Jarisch),[78] is treated simultaneously with other antihypertensive medications, or has concurrent myocardial or cerebral ischemia. Even transient hypotension in these situations can have catastrophic consequences.

   b. Nitroprusside promotes baroreflex activation, causing tachycardia that can exacerbate acute coronary syndromes and heart failure. Moreover, renin-angiotensin-aldosterone system stimulation blunts the antihypertensive efficacy because of increased vasoconstriction and sodium retention.

   c. Nitroprusside infusion requires invasive monitoring of BP in an intensive care unit setting, which

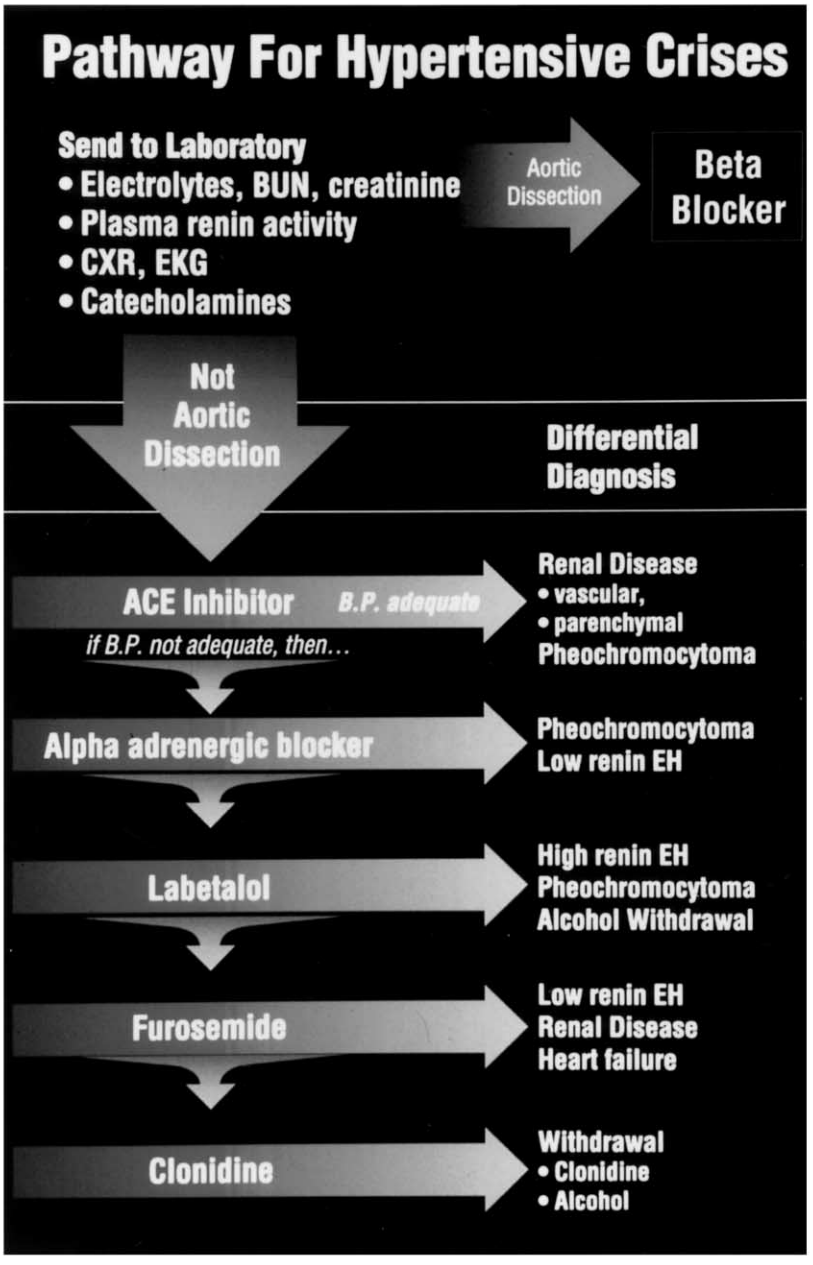


**FIG. 4.** Algorithm for the treatment of a hypertensive crisis. The blood pressure (BP) response to prototypic antihypertensive agents provides information that may direct further evaluation and treatment. CXR = chest x-ray; EKG = electrocardiogram; EH = essential hypertension.

may not otherwise be required. This adds significantly to the cost and morbidity of treatment.

d. Unlike the specifically targeted agents used in this treatment algorithm, empiric treatment with nitroprusside does not elucidate the pathophysiologic mechanism of hypertension, and it does not provide information that may advance the differential diagnosis of possible curable causes.

e. Patients must eventually be treated with oral antihypertensive medications. Nitroprusside treatment may delay the selection of appropriate oral therapy. Moreover, concurrent use of nitroprusside with other drugs may cause hemodynamic instability.

f. Nitroprusside can be toxic, especially in acutely ill patients, and its vasodilating properties cannot be dissociated from this toxicity. Upon its infusion, nitroprusside dissociates immediately, forming cyanide (CN) and the vasodilator nitric oxide (NO). Unlike the organic nitrates (eg, nitroglycerin), which require specific thiol-containing compounds to form NO, nitroprusside spontaneously generates this product and, therefore, can be considered a prodrug for NO and CN.[40] Both NO and CN are cleared by nonenzymatic routes. Five CN molecules are released by each nitroprusside molecule. These react with methemoglobin to produce cyanohemoglobin and the

remaining CN radicals are converted to thiocyanate in the liver. Cyanide toxicity can occur when sulfur stores are reduced by malnutrition, diuretic use, or surgery, or at high nitroprusside infusion rates (30 to 120 μg/kg/min). Regardless of the total dose or infusion rate, patients with central nervous system dysfunction, cardiovascular instability, and lactic acidosis should be considered to have CN toxicity. Treatment includes hydroxycobalamin and sodium thiosulfate infusions, which binds CN and facilitates renal excretion.[40] Thiocyanate, formed by the combination of endogenous thiosulfate and CN, is eliminated by the kidneys. Accumulation and toxicity may occur within 3 to 6 days in chronic renal failure patients. Its removal is facilitated by dialysis.

## Summary

The spectrum of disorders associated with an elevated BP encompasses chronic uncomplicated hypertension and the hypertensive crises. Although these syndromes can vary widely in their presentations, clinical courses, and outcomes, they share pathophysiologic mechanisms and, consequently, exhibit similar therapeutic responses to specifically targeted antihypertensive drug types. Accordingly, a similar conceptual framework can be applied to their analysis and treatment. The PRA measurement provides important information regarding the pathophysiology of hypertension in the individual patient with hypertension and, thus, plays an important role in the selection of effective drug treatment by defining at the outset the presence and degree of either sodium volume-mediated (V) hypertension (PRA $<0.65$ ng/mL/h) instead of renin-mediated (R)-mediated hypertension (PRA $\geq 0.65$ ng/mL/h). Because there are also two basic classes of antihypertensive drugs, the primary correct treatment of every form differs.

Although the relatively brief period (24 to 48 h) required for reporting plasma renin measurements is appropriate for the patient with chronic uncomplicated hypertension, it does not meet the requirement for immediate treatment in hypertensive crises. To accommodate this requirement for rapid treatment, we define herein a rapid method of serially assessing drug type responsiveness in which specifically targeted antihypertensive agents from each drug class (ie, antirenin (R) drugs, and antisodium-volume (V) drugs) are evaluated by being administered in single file order. The depressor response or lack of it, to one representative agent of each specific drug class, administered individually over a relatively brief period in the acute care setting, provides rapid insight into the mechanisms of hypertension that can facilitate further diagnostic evaluation and targeted treatment. For example, BP reduction after a dose of an ACE inhibitor defines renin-angiotensin-dependent hypertension, whereas a lack of BP response to this drug class excludes a predominant role of this mechanism, and suggest a sodium-volume mechanism. At the same time, this new strategy avoids the use of nitroprusside and dihydropyridine CCB, which can lower BP but delay definitive diagnosis and treatment while imposing added risks, especially in certain critical situations, ie, aortic dissection, acute MI, or cerebral hemorrhage.

## References


1. Bennett N, Shea S: Hypertensive emergency: case criteria, sociodemographic profile, and previous care of 100 cases. Am J Pub Health 1988;78:636–640.
2. Gifford R: Management of hypertensive crises. JAMA 1991;266: 829–835.
3. Grossman E, Messerli FH, Grodzicki T, Kowey P: Should a moratorium be placed on sublingualnifedipine capsules given for hypertensive emergencies and pseudoemergencies (see comments). JAMA 1996;276:1328–1331.
4. The Joint National Committee on Prevention Detection, and Treatment of High Blood Pressure: The sixth report of the joint national committee on prevention, detection and treatment of high blood pressure. Arch Intern Med 1997;157:2413–2446.
5. Zampaglione B, Pascale P, Marchisio M, Cavallo-Perin P: Hypertensive urgencies and emergencies: prevalence and clinical presentation. Hypertension 1996;27:144–147.
6. Laragh JH: Vasoconstriction-volume analysis for understanding and treating hypertension: the use of renin and aldosterone profiles. Am J Med 1973;55:261–274.
7. Laragh JH, Sealey JE, Niarchos AP, Pickering TG: The vasoconstriction-volume spectrum in normotension and in the pathogenesis of hypertension. Fed Proc 1982;41:2415–2423.
8. Laragh JH: Laragh lessons for treating hypertension: Lesson XV Poisseuille's Law via renin system behavior creates the volume vasoconstriction equation that supports all normotension or hypertension. Am J Hypertens 2001;14:400–404.
9. Laragh JH, Sealey JE: The renin-angiotensin-aldosterone system and the renal regulation of sodium and potassium and blood pressure homeostasis, *in* Windhager EE (ed): Handbook of Renal Physiology, New York, Oxford University Press, 1992, 1409–1541.
10. Laragh JH, Ulick S, Januszewicz V, Kelly WG, Lieberman S: Electrolyte metabolism and aldosterone secretion in benign and malignant hypertension. Ann Intern Med 1960;53:259–272.
11. Case DB, Atlas SA, Sullivan PA, Laragh JH: Acute and chronic treatment of severe and malignant hypertension with the oral angiotensin-converting enzyme inhibitor captopril. Circulation 1981;64: 765–771.
12. Vaughan C, Dealnty N: Hypertensive emergencies. Lancet 2000; 356:411–417.
13. Laragh JH: Laragh's lessons in pathophysiology for treating hypertension: Lessons XVI–XVIII, renin testing identifies two types of hypertension sodium volume V mediated (PRA $<0.65$) and renin R mediated (PRA $>0.65$) each correctly treated with anti-V or anti-R drugs, respectively. Am J Hypertens 2001;14:491–503.
14. Davis BA, Crook JE, Vestal RE, Oates JA: Prevalence of renovascular hypertension in patients with grade III or IV hypertensive retinopathy. N Engl J Med 1979;301:1273–1276.
15. Wallace J, Levy LL: Blood pressure after stroke. JAMA 1981;246: 2177–2180.
16. Powers W: Acute hypertension after stroke: the scientific basis for treatment decisions. Neurology 1993;43:461–467.
17. Strandgaard S: Autoregulation of cerebral blood flow in hypertensive patients: the modifying influence of prolonged antihypertensive treatment on the tolerance to acute, drug-induced hypotension. Circulation 1976;53:720–727.
18. Calhoun D, Oparil S: Treatment of hypertensive crisis. N Engl J Med 1990;323:1177–1183.
19. Vidt D: Emergency room management of hypertensive urgencies and emergencies. J Clin Hypertens 2001;111:158–164.

20. Symon L, Crockard HA, Dorsch NW, Branston NM, Juhasz J: Local cerebral blood flow and vascular reactivity in a chronic stable stroke in baboons. Stroke 1975;6:482–492.
21. Brott N, Lu M, Kothari R, Fagan SC, Frankel M, Grotta JC: Hypertension and its treatment in the NINDS rt-PA stroke trial. Stroke 1998;29:1504–1509.
22. Kaste M, Fogelholm R, Erila T, Palomaki H, Murros K, Rissanen A: A randomized, double-blind, placebo-controlled trial of nimodipine in acute ischemic hemispheric stroke. Stroke 1994;29:1504–1509.
23. Lisk D, Grotta J, Lamki L, Tran H, Taylor J, Molony D: Should hypertension be treated after acute stroke?: a randomized controlled trial using single photon emission computed tomography. Arch Neurol 1993;50:855–862.
24. Muller F, Lartaud I, Bray L, Atkinson J, Janian P, Burlet C: Chronic treatment with the angiotensin I converting enzyme inhibitor, perindopril, restores the lower limit of autoregulation of cerebral blood flow in the awake renovascular hypertensive rat. J Hypertens 1990; 8:1037–1042.
25. Ram C, Meese R, Kaplan N, Devous MS, Forland S, Cutler R: Antihypertensive therapy in the elderly. Effects on blood pressure and cerebral blood flow. Am J Med 1987;82:53–57.
26. Adams R, Powers W: Management of hypertension in acute intracerebral hemorrhage. Crit Care Clin 1997;13:131–161.
27. Feigin V, Rinkel G, Algra A, Vermeulen M, vanGijn J: Calcium antagonists in patients with aneursymal subarachnoid hemorrhage: a systematic review. Neurology 1998;50:876–883.
28. Radhakrishnan D, Menon D: Haemodynamic effects of intravenous nimodipine following aneurysmal subarachnois hemorrhage: implications for monitoring. Anesthesia 1997;52:489–500.
29. Porchet F, Chiolero R, de Tribolet N: Hypotensive effect of nimodipine during treatment for aneurysmal subarachnoid hemorrhage. Acta Neurochir(Wien) 1995;137:62–69.
30. Hayashi M, Kobayashi H, Kawano H, Handa Y, Hirose S: Treatment of systemic hypertension and intracranial hypertension in cases of brain hemorrhage. Stroke 1988;19:314–321.
31. Haley EJ, Kassell N, Torner J: A randomized controlled trial of high-dose intravenous nicardipine in aneurysmal subarachnoid hemorrhage: a report of the Cooperative Aneurysm study. J Neurosurg 1993;78:537–547.
32. Kincaid-Smith P: Malignant hypertension: mechanisms and management. Pharmacol Ther 1980;9:245–269.
33. Buhler FR, Laragh JH, Vaughan EDJ, Brunner HR, Gavras H, Baer L: Antihypertensive action of propranolol: specific anti-renin responses in high and normal renin forms of essential, renal, renovascular and malignant hypetension. Am J Cardiol 1973;35:511–522.
34. Tifft CP, Gavras H, Kershaw GR, Gavras I, Brunner HR, Liang C: Converting enzyme inhibition in hypertensive emergencies. Ann Intern Med 1979;90:43–47.
35. Hirschl M, Binder M, Bur A, Brunner M, Mullner M, Sterz F: Clinical evaluation of different doses of intravenous enalaprilat in patients with hypertensive crises. Arch Intern Med 1995;155:2217–2223.
36. Griffith D, James I, Newbury P, Woollard M: The effect of beta-adrenergic receptor blocking drugs on cerebral blood flow. Br J Clin Pharmacol 1979;7:491–494.
37. Pretre R, von Segresser L: Aortic dissection. Lancet 1997;349: 1461–1464.
38. Wheat M, Palmer R: Treatment of dissecting aneurysms of the aorta without surgery. J Thoracic and Cardiovasc Surg 1965;50:364–373.
39. Palmer R: *in* Laragh JH, and Seldon DF (eds): Frontiers in Hypertension Research: Vascular compliance and pulsatile flow as determinants of vascular injury, New York, Springer-Verlag, 1981; 396–400.
40. Friedrich J, Butterworth JI: Sodium nitroprusside: twenty years and counting. Anesth Analg 1995;81:152–162.
41. Palmer R, Lasseter K: Nitroprusside and aortic dissecting aneurysm. N Engl J Med 1976;294:1403–1404.
42. Rouby J, Gory G, Bourrelli B, Glaser P, Viars P: Resistance to sodium nitroprusside in hypertensive patients. Crit Care Med 1982; 10:301–303.
43. Shepherd A, Irvine N: Differential hemodynamic and sympathoadrenal effects of sodium nitroprusside and hydralazine in hypertensive subjects. J Cardiovasc Pharmacol 1986;8:527–533.
44. Woodside JJ, Garner L, Bedford R, Sussman M, Miller E, Longnecker D: Captopril reduces the dose requirement for sodium nitroprusside-induced hypotension. Anesthesiology 1984;80:413–417.
45. White S, Hall J: Control of hypertension with nifedipine in the setting of aortic dissection. Chest 1985;88:781.
46. Ruzicka M, Leenen F: Relevance of intermittent increases in sympathetic activity for adverse outcome on short-acting calcium antagonists, Brenner BM (ed): Hypertension: Pathophysiology, Diagnosis, and Management, New York, Raven Press, 1995; 2815–2825.
47. Agency for Health Care Policy and Research (abstr.) Heart Failure: Management of patients with left-ventricular systolic dysfunction. 1994;11 (94-0612).
48. Pickering TG, Blumenfeld JD: Renovascular hypertension, *in* Brenner BM (ed): The Kidney, Philadelphia, WB Saunders Co, 1999; 2007–2034.
49. Swedberg K, Eneroth P, Kjekshus J, Wilhelmsen L: Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality. Circulation 1990;82: 1730–1736.
50. Vantrimpont P, Rouleau J, Ciampi A, Harel F, DeChamplain J, Bichet D: Two-year time course and significance of neurohumoral activation in survival and ventricular enlargement (SAVE) study. Eur Heart J 1998;19:1552–1563.
51. Packer M, Medina N, Yushak M: Efficacy of captopril in low renin congestive heart failure: Importance of sustained reactive hyperreninemia in distinguishing responders from nonresponders. Am J Cardiol 1984;54:771–777.
52. Packer M, Lee WH, Kessler P: Preservation of glomerular filtration rate in human heart failure by activation of the renin-angiotensin system. Circulation 1986;74:766–774.
53. Cody RJ, Covit AB, Schaer GL, Laragh JH, Sealey JE, Feldschuh J: Sodium and water balance in chronic congestive heart failure. J Clin Invest 1986;77:1441–1452.
54. Schrier RW: Pathogenesis of sodium and water retention in high-output and low-output cardiac failure, nephrotic syndrome, cirrhosis, and pregnancy (1). N Engl J Med 1988;319:1065–1072.
55. Schrier RW: Pathogenesis of sodium and water retention in high-output and low-output cardiac failure, nephrotic syndrome, cirrhosis, and pregnancy (2). N Engl J Med 1988;319:1127–1134.
56. Francis G, Cohn J, Johnsong G, Rector T, Goldman S, Simon A: Plasma norepinephrine, plasma renin activity, and congestive heart failure. Circulation 1993;87:VI-40–VI-48.
57. ACE inhibitor myocardial infarction collaborative group: Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of the individual data from 100,000 patients in randomized trials. Circulation 1998;97:2202–2212.
58. Pitt B, Poole-Wilson PA, Segal R, Martinez FA, Dickstein K, Camm AJ: Effort of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial—the losartan heart failure survival study ELITE II. Lancet 2000;355: 1582–1587.
59. Pitt B, Segal R, Martinez FA, Meurers G: Randomized trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). Lancet 1997; 349:747–752.
60. Pitt B, Zannad F, Remme W, Cody R, Castaigne A, Perez A: The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med 1999;341:709–717.
61. van Vliet A: Spironolactone in congestive heart failure refactory to high dose loop diuretics and low dose angiotesin converting enzyme inhibitor. Am J Cardiol 1993;71:21A–29A.

62. Blumenfeld JD, Sealey JE, Alderman MH, Cohen H, Lappin R, Catanzaro DF, Laragh JH: Plasma renin activity in the emergency department and its independent association with acute myocardial infarction. Am J Hypertens 2000;13:855–863.
63. Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJJ, Cuddy TE, Davis BR, Geltman EM, Goldman S, Flaker GC: Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. N Engl J Med 1992;327:669–677.
64. Blumenfeld JD, Sealey JE, Mann SA, Bragat A, Marion R, Pecker MS, Sotelo J, August P, Pickering TG: Beta-adrenergic receptor blockade as a therapeutic approach for suppressing the renin-angiotensin-aldosterone system in normotensive and hypertensive subjects. Am J Hypertens 1999;12:451–459.
65. Gottlieb SS, McCarter RJ, Vogel RA: Effect of beta-blockade on mortality among high-risk and low risk patients after myocardial infarction. N Engl J Med 1998;339:489–497.
66. Chiarello M, Gold H, Leinbach R, Davis M, Maroko P: Comparison between the effects of nitroprusside and nitroglycerin on ischemic injury during acute myocardial infarction. Circulation 1976;54:766–773.
67. Roberts R: Review of calcium antagonist trials in acute myocardial infarction. Clin Cardiol 1989;12:III41–III47.
68. Becker RC, Caputo R, Ball S, Corrao JM, Baker S, Gore JM: Hemorrhagic potential of combined diltiazem and recombinant tissue-type plasminogen activator administration. Am Heart J 1993; 126:11–14.
69. Legault C, Furberg CD, Wagenknecht LE, Rogers AT, Stump DA, Coker L: Nimodipine neuroprotection in cardiac valve replacement: report of an early terminated trial. Stroke 1996;27:593–598.
70. Hynynen M, Kuitunen A, Salmenpera M: Surgical bleeding and calcium antagonists. Br Med J 1996;312:313.
71. Lange R, Hillis L: Cardiovascular complications of cocaine use. N Engl J Med 2001;345:351–358.
72. Pitts W, Lange R, Cigarroa J, Hillis L: Cocaine-induced myocardial ischemia and infarction: pathophysiology, recognition, and management. Prog Cardiovasc Dis 1997;40:65–76.
73. Poon J, van den Buuse M: Autonomic mechanisms in the acute cardiovascular effects of cocaine in conscious rats. Eur J Pharmacol 1998;363:147–152.
74. Working group on high blood pressure in pregnancy: Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Am J Obstet Gynecol 2000; 183:S1–S22.
75. Witlin AG, Sibai BM: Magnesium sulfate therapy in preeclampsia and eclampsia. Obstet Gynecol 1998;92:883–889.
76. Pryde PG, Sedman AB, Nugent CE, Barr M, Jr: Angiotensin-converting enzyme inhibitor fetopathy. J Am Soc Nephrol 1993;3: 1575–1582.
77. Cockburn J, Moar V, Ouensted M, Redman C: Final report of study on hypertension during pregnancy: the effects of specific treatment in the growth and development of the children. Lancet 1982;1:647–649.
78. Wasserstrum N: Nitroprusside in preeclampsia. Circulatory distress and paradoxical bradycardia. Hypertension 1991;18:79–84.
79. Blumenfeld JD, Laragh JH: Renin system analysis: a rational method for the diagnosis and treatment of the individual patient with hypertension [In Process Citation]. Am J Hypertens 1998;11:894–896.
80. Bolli P, Awann F, Buhler FR: Acute hypotensive response to post-synaptic alpha-blockade with prazosin in low and normal renin hypertension. J Cardiovasc Pharmacol 1980;2:S399–S405
81. Atkin S, Jaker M, Beaty P, Quadrel M, Cuffie C, Soto-Greene M: Oral labetalol versus oral clonidine in the emergency treatment of severe hypertension. Am J Med Sci 1992;303:9–15.