Hypertension

NEW CONCEPTS IN THE EMERGENCY DEPARTMENT TREATMENT OF HYPERTENSION

BY

GARY REED, M.D.

Medical Grand Rounds
University of Texas Health Science Center at Dallas
Southwestern Medical School
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INTRODUCTION

During the past several years, tremendous advances have been made in the treatment of hypertension. The risks of the disease and the benefits of chronic therapy are becoming clear (1,2,3). Advances in the pathophysiology of hypertension and its complications, the number of safe and effective antihypertensive drugs now available and the recent pressure exerted on the medical community toward cost containment have raised many questions regarding the acute treatment of this disease. This discussion will attempt to review some of the recent advances and controversies in the emergency department treatment of hypertension.

HYPERTENSIVE EMERGENCIES AND URGENCIES

Hypertension is a very common condition; consequently, it is frequently encountered by emergency physicians in acutely ill patients as a primary or secondary problem. Patients who present to an emergency department with hypertension can usually be placed into one of three categories: 1) hypertensive emergency, 2) hypertensive urgency or 3) hypertension not requiring immediate attention or treatment.

Patients with marked or sudden elevations in blood pressure that pose an immediate threat to the heart, brain or kidney are considered to have a hypertensive emergency (Figure 1).

Figure 1

HYPERTENSIVE EMERGENCIES

1. Hypertensive encephalopathy
2. Pheochromocytoma crisis
3. Acute pulmonary edema associated with severe hypertension
4. Intracranial hemorrhage associated with severe hypertension
5. Acute dissecting aneurysm of the aorta
6. Severe hypertension associated with significant postoperative bleeding
7. MAO inhibitor crisis
8. Toxemia of pregnancy
9. Severe hypertension with myocardial infarction
10. Some cases of malignant hypertension

These patients need immediate treatment aimed at lowering blood pressure to a reasonable level within minutes (up to one hour). The emergent nature of these conditions and the tenuous hemodynamic status of most of the patients usually mandate treatment that includes parenteral medications that allow rapid reduction of blood pressure over a few minutes. Nitroprusside, diazoxide, and trimethaphan have been the drugs most used for these conditions over the past several years.

In the past, definitions of hypertensive emergency have usually included a level of diastolic pressure above which the patient was considered to be in immediate danger. Over the last few years, this concept has changed as our understanding of the pathophysiology of hypertensive crisis has improved. For example, it is now known that the rate at which the hypertension develops is more important in most patients than the absolute level of blood pressure (4). Normotensive women who develop hypertension during pregnancy or patients who develop hypertension acutely with glomerulonephritis can develop severe hypertensive encephalopathy at levels of blood pressure most internists would not consider excessive (less than 115 mm Hg). These patients obviously need immediate, aggressive treatment to avoid mortality or serious morbidity. On the other hand, most physicians have seen patients with longstanding severe hypertension and diastolic blood pressures of greater than 140 mm Hg with no symptoms or other evidence of acute decompensation. These patients with severe chronic hypertension are able to tolerate such high pressures because of adaptive processes in the brain (5) and other vital organs that take months or even years to develop. Because of the above observations, there has been decreasing emphasis on the absolute level of blood pressure and more concern with the condition of the patient at the time of the visit.

Patients with hypertensive urgency, on the other hand, present with hypertensive complications or other conditions that mandate an immediate reduction of blood pressure but not at such a rapid rate as above with the attendant risks of parenteral medications and sudden blood pressure reduction. Generally these patients need their blood pressure lowered over several hours (up to 24 hours). Some examples of hypertensive urgencies can be found in Figure 2.

Figure 2

EXAMPLES OF HYPERTENSIVE URGENCIES

1. Accelerated hypertension
2. Perioperative hypertension
3. Severe hypertension in patients needing semi-emergent surgery
4. Moderate to severe hypertension with angina pectoris
5. Severe hypertension with rapidly progressing renal insufficiency or retinopathy
6. Acutely symptomatic hypertension without evidence of hypertensive emergency

Again, note that these patients have some reason other than the absolute level of hypertension that mandates blood pressure reduction. One reason that this group has become important in the past few years is that antihypertensive drugs are now available that can safely and effectively lower blood pressure over several hours. Also, these new regimens allow some patients to be treated and released from the emergency department with appropriate follow-up. Prudent medical judgement, however, is important in determining which patients need hospitalization. When doubt exists regarding the compliance with drug therapy over the subsequent few days or the severity of underlying hypertensive complications, the patient should be hospitalized.

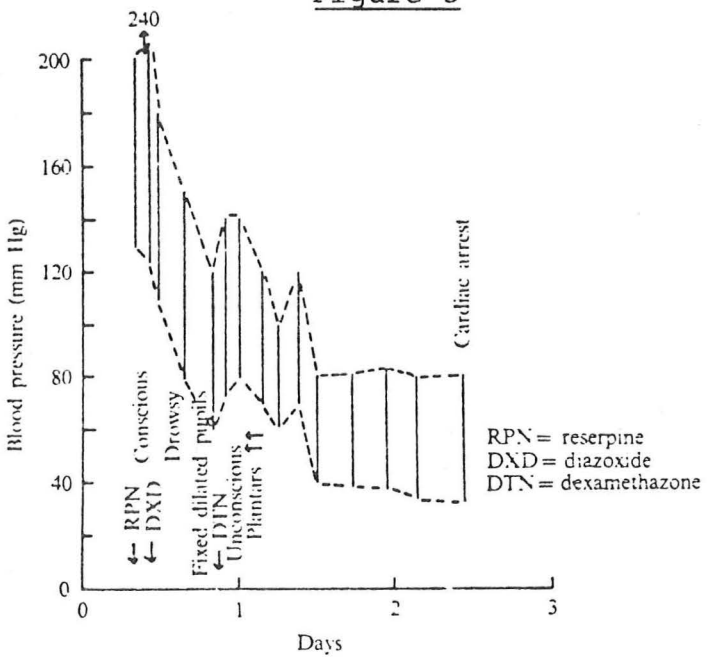
The final group of patients encountered in the emergency department are those who have hypertension which may be severe but no indication exists for acute or subacute blood pressure reduction. Most of these patients are chronically hypertensive and present with emergency problems unrelated to hypertension. Many are noncompliant with previous antihypertensive regimens. Generally, these patients need to be restarted on appropriate therapy and follow-up arranged within a few days. The distinction between this group of patients and those with hypertensive urgency is often indistinct. For example, there is no data that suggests a certain level of blood pressure that in itself mandates immediate therapy. Until such studies are published, therapy for each patient must be individualized and caution exercised when patients are treated or not treated immediately.

When making a decision as to the necessity for immediate hypotensive therapy for patients with hypertension, one must consider the risks of all options. There is no doubt that the

presence of hypertension creates a risk for major complication involving the heart, central nervous system and kidneys. However, predicting when these complications will occur in a given patient is impossible. Most patients with hypertension need effective chronic therapy, not acute therapy, to reduce the risk of complications. The possibility of developing a major complication in the near future mandates acute therapy in some patients, but clinical judgement and experience is presently the only way now available to select these patients.

When the acute treatment of hypertension is undertaken, one assumes that the reduction in blood pressure reduces the risk of a major complication. Unfortunately, this acute hypotensive therapy carries significant risk, primarily that of hypoperfusion of vital organs such as the brain and kidneys. An example of a complication of such therapy is illustrated in Figure 3 (6). In this patient, rapid blood pressure reduction resulted in serious brain ischemia and eventually death.

Figure 3



Frequently, those patients most likely to quickly develop a complication of acute blood pressure elevation are also at high risk for complications of acute blood pressure reduction, e.g., patients with significant cerebrovascular disease and elderly patients. Until predictors of the immediate risk of blood pressure elevation are clearly defined, the decision to treat or not to treat will remain a difficult one to make in any individual patient.

OLDER DRUGS USED IN THE TREATMENT OF HYPERTENSIVE URGENCIES

Hydralazine

Parenteral hydralazine has been used for many years in the treatment of hypertensive emergencies and urgencies, especially those related to pregnancy. It is an arterial vasodilator with a hypotensive effect usually seen within 30 minutes of injection. Generally, the drug is given in doses of 10 mg to 50 mg intramuscularly or 5 mg to 20 mg intravenously. Hydralazine rarely causes hypotension when used alone except occasionally when injected rapidly by the intravenous route. Another advantage is that it maintains blood flow to the kidneys and brain.

Hydralazine has several disadvantages limiting its use in medical patients with hypertensive urgencies. The maximum effect of the drug may not be seen for 1 or 2 hours making it no better than most of the oral drugs discussed below yet still having the risk and discomfort of parenteral injection. It also causes activation of the sympathetic nervous system because of its direct vasodilating effects. This can lead to an increase in myocardial oxygen demand and precipitate angina pectoris or myocardial infarction in patients with coronary artery disease (7).

Methyldopa

Methyldopa can be given intravenously in doses of 250 mg to 500 mg. It has a delayed onset of action (2 to 3 hours) and hypotensive responses are not as consistent as with reserpine (8) or other available agents. Its main side effect is drowsiness, and it should not be given to patients with hepatic disease.

Reserpine

Parenteral reserpine has been used in the past before better parenteral antihypertensive agents were available. Although effective in intramuscular doses of 1 mg to 5 mg, it has a delayed onset of action (2 to 3 hours), can cause a profound depression of mental status and may cause bradycardia. It is not recommended for the acute treatment of hypertension now.

Furosemide

Intravenous furosemide has been used in the acute treatment of hypertension in the past, usually in conjunction with other antihypertensive agents, such as diazoxide, that induce sodium retention. It continues to be used as adjunctive therapy in patients with hypertensive emergencies and urgencies, but its acute antihypertensive action when used alone is not very good (9).

NEWER DRUGS USED IN THE TREATMENT OF HYPERTENSIVE URGENCIES

Over the last few years, several drugs have become available that are useful in oral form in treating hypertensive patients who need blood pressure reduction acutely. These drugs are most useful in those patients whose blood pressure needs to be lowered over several hours and does not warrant the risk of acute blood pressure reduction with parenteral agents. These drugs have several advantages over conventional antihypertensive agents that have been used in emergency treatment. They are less expensive to administer and do not have the discomfort and risk of intravenous infusion. Constant hemodynamic monitoring and nursing personnel are not necessary thereby negating the need for an intensive care unit bed for most patients with hypertensive urgencies. With some of the drugs, blood pressure can be gradually reduced avoiding the risk of sudden reductions in perfusion pressure to vital organs. Finally, the drug that is used to lower the blood pressure effectively can be used to start chronic treatment and hospitalization can be avoided in carefully selected patients.

As a rule, the oral form of any drug is not considered adequate treatment for real hypertensive emergencies. Parenteral administration of one of the traditional medications should be utilized for these patients until adequate studies have been done on the newer drugs.

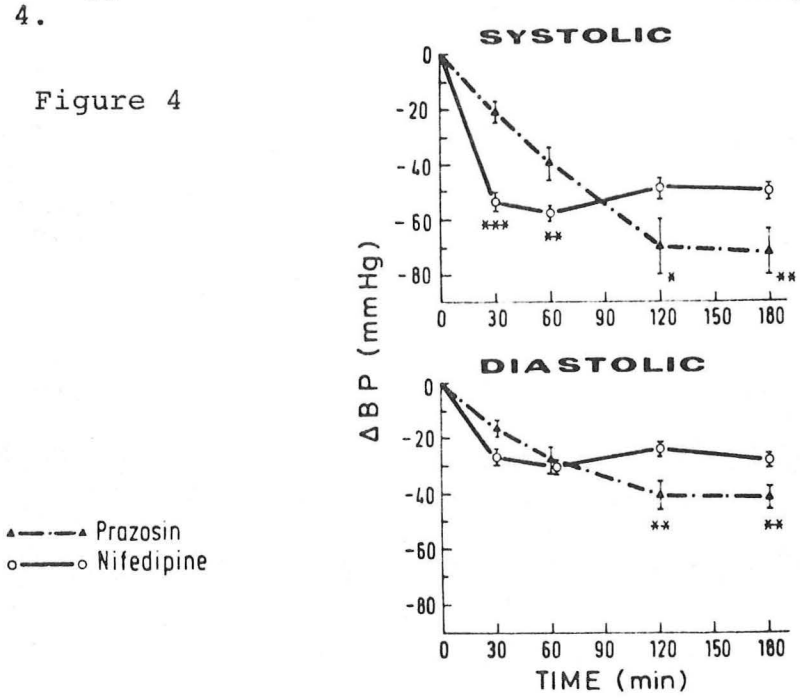
Prazosin

Prazosin is an antihypertensive agent that reduces peripheral vascular resistance by selectively blocking alpha 1-adrenergic receptors. This selective blockade allows the drug to lower vascular resistance without causing the reflex tachycardia and hyperreninemia seen with many other vasodilators (10). It is effective in treating mild, moderate or severe hypertension and is particularly useful in patients with impaired renal function (11), asthma, diabetes mellitus (12), and heart block.

Prazosin has been used to acutely treat hypertension by several groups. Hayes (13) reported 19 patients, 25 to 64 years of age, who were treated with a single large dose (usually 5 mg) after presenting with one of the following indications for therapy: 1) diastolic blood pressure of 130 mm Hg or greater, 2) postoperative hypertension, 3) hypertension in a patient needing an invasive procedure, and hypertension in patients needing peritoneal dialysis. Blood pressure fell in these patients from 192/118 mm Hg to 157/100 mm Hg after 60 to 120 minutes. Blood pressure began to fall within 30 minutes of the oral dose.

In 1983, Yagil, et al . (14), compared the effects of prazosin (2 mg) to oral nifedipine (10 mg) in 26 patients with uncontrolled hypertension. The results of this study are shown in Figure 4.

Figure 4



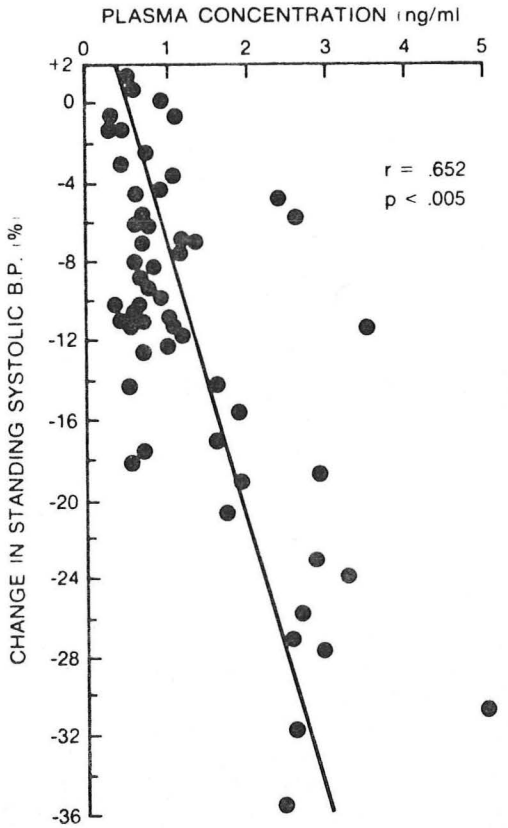
Both drugs caused a significant decrease in blood pressure that lasted at least 3 hours. Prazosin caused a more gradual reduction in pressure, but was equal to nifedipine in efficacy at hours 2 and 3. Diastolic blood pressure in five of the 13 patients that received prazosin fell to less than 80 mm Hg after 2 hours. The only side effect that developed was postural hypotension which developed in 9 patients.

Side effects which must be monitored include orthostatic hypotension, dizziness, headache, drowsiness, and weakness. Orthostatic hypotension is frequent and exacerbated if other antihypertensive agents such as diuretics or beta-blockers are also used.

Clonidine

Clonidine hydrochloride is a potent centrally acting alpha-adrenergic agonist that has been used for many years in treating mild, moderate and severe hypertension. It reduces blood pressure by stimulating postsynaptic alpha-adrenergic receptors in the depressor site of the vasomotor center of the locus coeruleus of the medulla oblongata resulting in a decreased sympathetic outflow from this region (15). This leads to diminished efferent sympathetic neuronal vasoconstrictor tone to the heart, kidneys and peripheral vasculature. The drug is rapidly absorbed from the gastrointestinal tract. Antihypertensive activity begins within 30 to 60 minutes of ingestion and peaks in 2 to 4 hours. The antihypertensive activity of the drug is closely related to the plasma concentration of the drug as illustrated in Figure 5 (16).

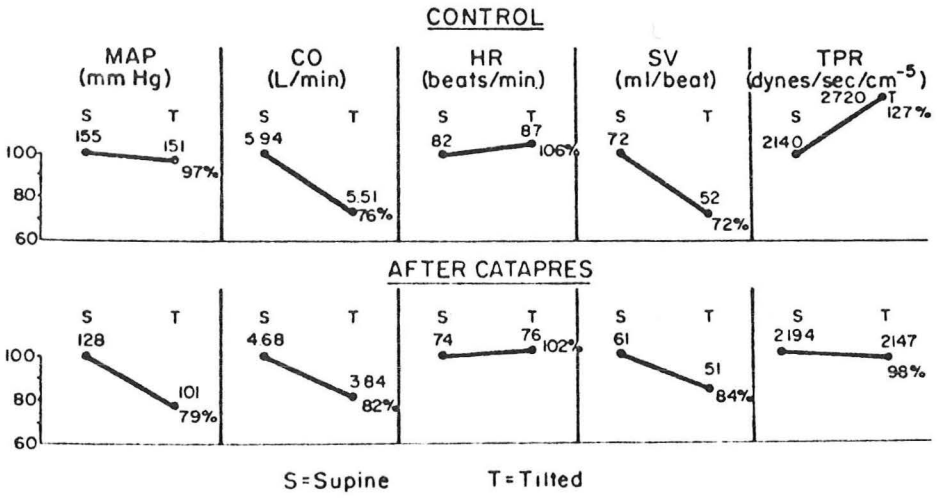
Figure 5



Percent decrease in standing systolic blood pressure as a function of plasma clonidine concentration.

The acute effects of clonidine in the supine position after an oral dose of 0.3 mg result in an average mean arterial blood pressure reduction of about 17% in hypertensive patients (17). Cardiac output and heart rate are reduced an average of approximately 21% and 10%, respectively. Stroke volume decreases an average of 15% while peripheral resistance does not change consistently. The hemodynamics of clonidine in the head up position are similar to the supine position except there is a significant reduction in total peripheral resistance (21%). These hemodynamic parameters are summarized in Figure 6 (17).

Figure 6



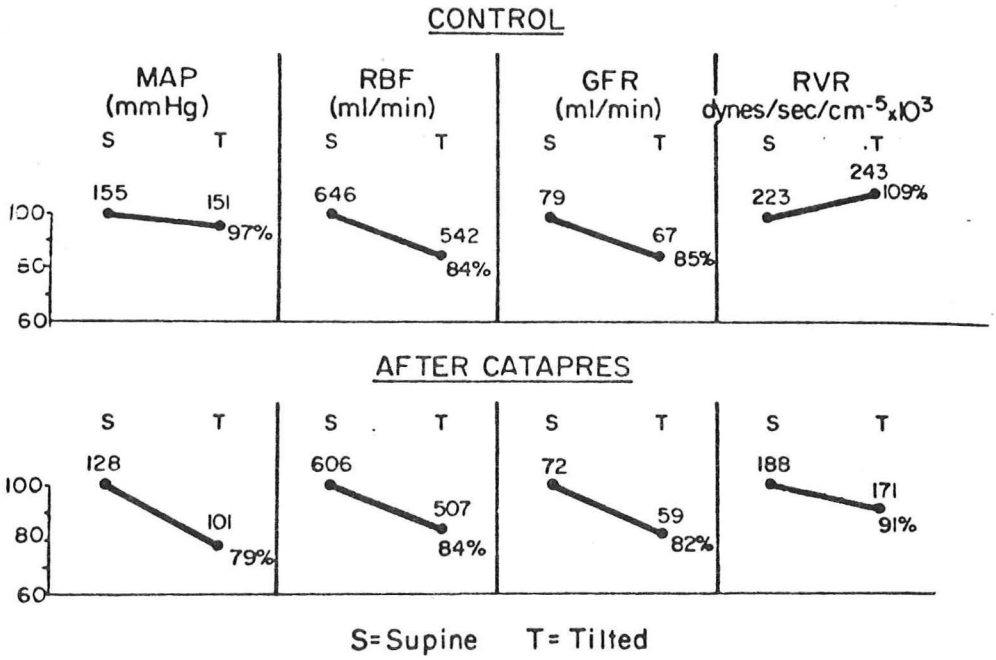
Cardiac hemodynamic effects of passive head-up tilting (45 degrees), control (above) and after clonidine (below).

The reduction in cardiac output is probably due to a combination of a decreased heart rate and a decreased venous return (decreased preload). There is no evidence that clonidine directly causes a decrease in myocardial contractility.

Masotti, et al. (18), have observed improvement in cardiac function after the intravenous injection of clonidine to patients with hypertensive emergencies. This improvement was manifested by a significant reduction of end-diastolic and end-systolic volumes and an increase in ejection fraction. Cardiac oxygen consumption was also reduced from 19.98 ± 5.03 ml per 100 g per minute to 5.81±2.92 (p 0.001).

The acute renal hemodynamics of clonidine are shown in Figure 7 (17).

Figure 7



Renal hemodynamic effects of passive head-up tilting (45 degrees), control (above) and after clonidine (below).

In the supine and head up positions, there are no significant alterations in glomerular filtration rate or renal blood flow. However, there is a significant decrease in renal vascular resistance in the head up position. Studies on the effects of clonidine on sodium balance have yielded different conclusions. Onesti, et al. (17), found a tendency toward sodium and chloride retention while others have found little effect on sodium excretion with acute administration of the drug (19). With chronic administration, sodium balance is probably not affected.

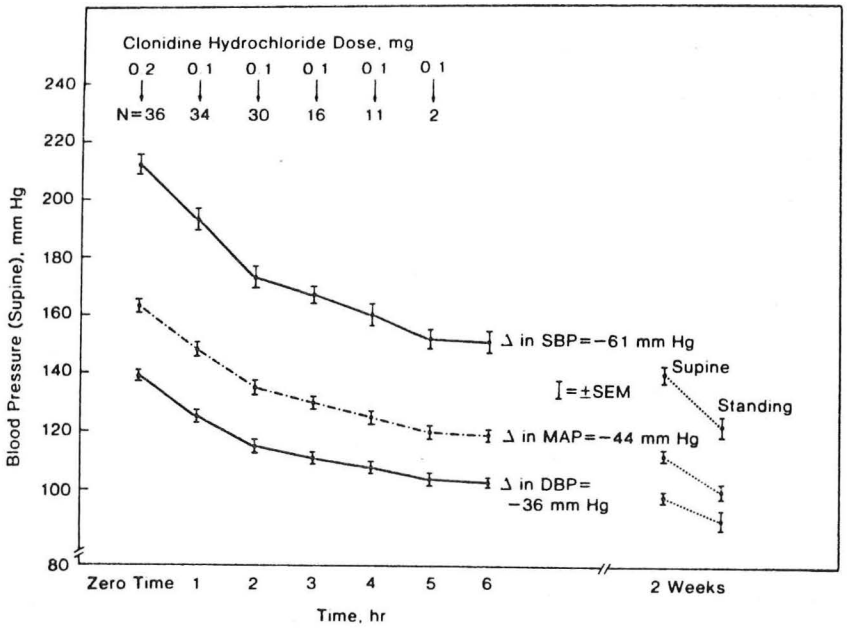
EFFICACY OF CLONIDINE LOADING

While intravenous clonidine has been used for several years in Europe for the treatment of hypertensive emergencies, Cohen and Katz (20) in 1978 were the first to describe a method of reducing blood pressure by oral clonidine loading. 15 patients were given 0.1 or 0.2 mg of oral clonidine followed by 0.1 mg

every hour until blood pressure had been lowered to a satisfactory level or the patient had received a maximum of 0.5 mg of the drug. 12 of the 15 patients had a significant reduction in mean arterial pressure (141 ± 2 to 108 ± 4 mm Hg). Heart rate was significantly reduced from 80 6 to 51 6 beats per minute.

In a later study, Anderson, et al. (21), used clonidine to treat 36 black patients with hypertensive urgencies and supine diastolic blood pressures above 120 mm Hg. These patients all had physical, laboratory or electrocardiographic evidence of hypertension related end organ damage. Patients were given 0.2 mg of clonidine initially followed by 0.1 mg every hour until the supine diastolic pressure was reduced by 20 mm Hg, the supine diastolic blood pressure dropped below 110 mm Hg or a maximum total dose of 0.7 mg of clonidine had been given. The blood pressure response to this regimen is depicted in Figure 8 (21).

Figure 8



Blood pressure response to clonidine loading.

One hour after the initial dose of 0.2 mg of clonidine, supine blood pressure fell from 212 (±22)/139 (±11) mm Hg to 193 (±25)/125(±13) mm Hg (p 0.05). N in the above figure represents

the number of patients receiving subsequent doses of clonidine. The blood pressure at 6 hours was 151(± 21)/103(± 11) which corresponds to a net reduction of 61 mm Hg in systolic blood pressure, 36 mm Hg in diastolic blood pressure and 44 mm Hg mean arterial pressure. The reduction in blood pressure was statistically significant every hour of the six hour study except hours five and six.

Finally, Spitalewitz, et al. (22), reported treating 20 patients with an oral clonidine loading regimen consisting of 0.2 mg initially followed by 0.1 mg or 0.2 mg at one hour then 0.1 mg hourly to a maximum dose of 0.8 mg. All patients had a fall in diastolic blood pressure to less than 100 mm Hg or a fall in mean arterial pressure of 30 mm Hg or more.

Although the gradual reduction in blood pressure allows for individualization of therapy with relative ease in most patients, the amount of oral clonidine required to lower severe elevations in blood pressure to acceptable levels varies from 0.1 mg to 0.8 mg. Despite this wide patient to patient variation, the mean total dose needed to lower blood pressure in the reported patients has been fairly consistent (0.32 mg to 0.45 mg).

ADVANTAGES OF CLONIDINE LOADING

Oral clonidine loading has several advantages in the treatment of hypertensive urgencies. It is very effective in lowering the blood pressure of most patients with hypertension. Blood Pressure can be lowered gradually over several hours in a smooth fashion thereby avoiding the risk of abrupt changes in perfusion pressure. Clonidine has a duration of action of 8 to 12 hours after the blood pressure has been lowered (21). After oral loading, the drug can be used for chronic therapy although the subsequent dose needed for control of blood pressure cannot be predicted from the amount of drug required for the initial titration of the blood pressure. As with other oral loading techniques, the cost and discomfort of intravenous infusion can be avoided. Constant cardiac and hemodynamic monitoring is not necessary.

The acute hemodynamic effects of clonidine make it a suitable drug for use in patients with congestive heart failure. Magorien, et al. (23), gave an oral, 0.2 mg dose of clonidine to 10 patients with moderately severe heart failure and found that peripheral blood flow was unaffected to the forearm, liver and kidney while mean systemic pressure and pulmonary capillary wedge pressure decreased by 14% and 27%, respectively. In other words, clonidine causes a significant reduction in left ventricular preload and afterload in patients with congestive heart failure.

The effects of clonidine on central and peripheral sympathetic activity make it useful in treating the severe hypertension that frequently accompanies opiate withdrawal (24,25,26). The constellation of signs and symptoms of these patients results from sympathetic over-activity and includes hypertension, anxiety, mydriasis, tachypnea, tachycardia and diaphoresis. While clonidine has no affinity for the opiate receptor, it does effectively modulate the increased sympathetic activity seen in patients withdrawing from a wide variety of narcotics including heroin, methadone, oxycodone and levorphanol. When treating these patients, the dosage and duration of treatment should be dictated by the drug to which the patient is addicted. Generally, 5 ug per kg per day in divided doses is enough. Therapy should be continued for 7 to 21 days depending on the addicting drug, then tapered to avoid the reappearance of sympathetic symptoms or hypertension. It is important to remember that clonidine does not treat the addiction, only the acute symptoms of withdrawal, so all patients need appropriate referral if treated and released from the emergency department.

SIDE EFFECTS

The side effects of oral clonidine loading are depicted in Figure 9.

Figure 9

SIDE EFFECTS OF CLONIDINE LOADING

1. Sedation
2. Dizziness
3. Bradycardia
4. Orthostasis

The principle side effect noted during oral clonidine loading is mild to moderate sedation which occurs in 20% to 45% of patients (27). Dizziness (non-orthostatic) has been reported in up to 13% of patients. Orthostatic symptoms are uncommon (less than 5%) although orthostatic changes in blood pressure are frequent.

Heart rate is generally reduced 10% to 40% after loading. Although this change has not been reported to cause any detrimental effects after oral loading, patients with a initial heart rate of 60 beats per minute or less, known sick sinus syndrome or any degree of atrioventricular block should have careful cardiac monitoring. Clonidine, and other sympathetic blocking agents, have been reported to precipitate symptomatic

bradycardia in patients with subclinical sick sinus syndrome who have used these drugs for the treatment of hypertension (28). Also, Thormann, et al. (29), reported 11 patients with a mean age of 60 years and a previous history suggestive of sinus node or conduction system disease who developed significant sinus node and conduction abnormalities after 0.15 mg of intravenous clonidine. Sinus node recovery time of one of their patients is illustrated in Figure 10 and the sinus node recovery times before and after intravenous clonidine for all the patients are shown in Figure 11. After the injection of clonidine, these authors also found a 12% (p 0.05) increase in the length of the sinus cycle and an 8% (p 0.05) decline in atrioventricular conduction capacity.

Figure 10

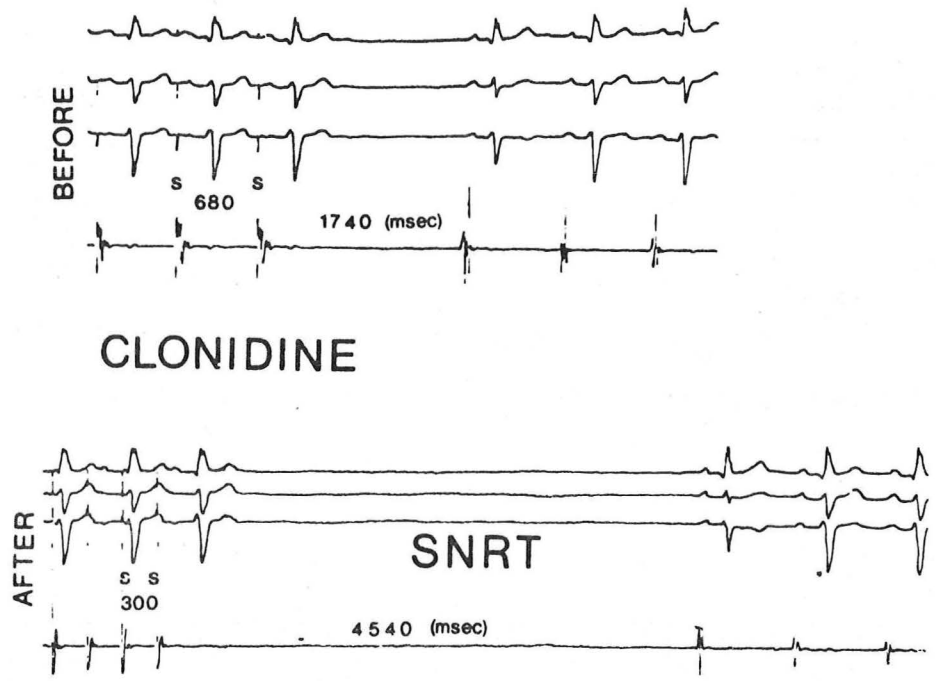
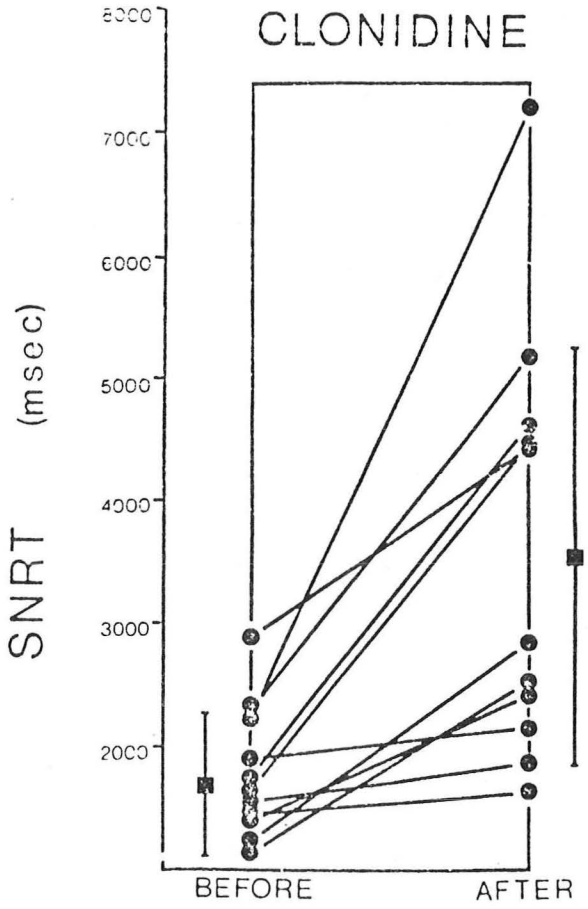


Figure 11



On the other hand, Toussaint, et al. (30), have recently reported that acute treatment of patients with a mean age of 69 years with 150 ug of intravenous clonidine resulted in no significant change in sinus cycle length, maximum corrected sinus node recovery time, estimated atrio-sinoatrial conduction time, premature atrial stimulation-response curve, conduction interval, anterograde conduction point, effective refractory period of the atrioventricular node and intraventricular conduction time.

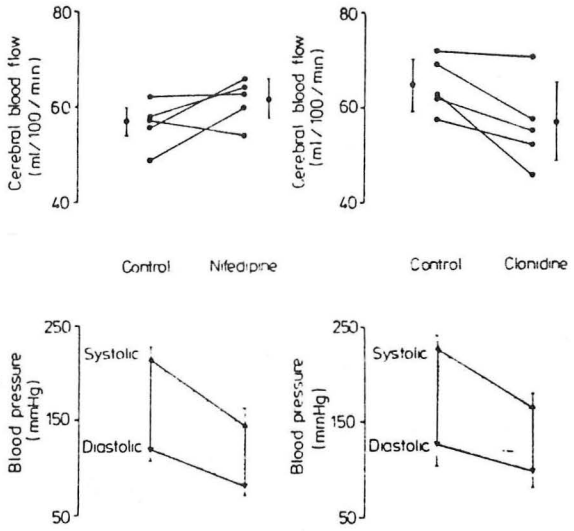
If serious and/or symptomatic bradycardia occurs during clonidine loading, atropine may be used in the standard doses.

Serious side effects are uncommon after clonidine loading and usually have resulted from excessive blood pressure reduction in patients with preexisting cerebrovascular disease. One patient reported by Spitalewitz (22) suffered a cerebrovascular

accident after a fall in blood pressure from 239/139 mm Hg to 150/110 mm Hg over three hours. Another patient from our emergency department also suffered a stroke several hours after his severely elevated blood pressure had been lowered utilizing clonidine. Both of these patients had a history of cerebrovascular disease manifested by transient ischemic attacks.

The direct effect of clonidine on global and regional cerebral blood flow is unknown. Bertel, et al. (31), reported a reduction of global cerebral blood flow in patients with hypertensive emergencies treated with intravenous clonidine (Figure 12). Whether this reduction was a direct effect of the drug or due to the rapid dropping of blood pressure in patients with altered cerebral autoregulation cannot be discerned.

Figure 12



Unpublished data from our lab indicate that the reduction in global cerebral blood flow seen with some patients after oral clonidine loading is probably due to the degree of lowering of the blood pressure. Whatever the reason, blood pressure should be lowered carefully and gradually in patients with known or suspected cerebrovascular disease unless an overriding reason for immediate blood pressure lowering exists. In these non-emergent cases, mean arterial pressure should not be lowered acutely below approximately 120 mm Hg to avoid global or focal brain ischemia. Later, blood pressure can be reduced gradually over several

hours, days or even weeks depending on the patients age duration of hypertension and degree of fixed cerebrovascular disease.

Hypotension has been reported to occur in less than 5% of patients who are loaded orally with clonidine. If hypotension does occur, proper positioning of the patient and volume infusion with normal saline generally is sufficient to raise the blood pressure to an acceptable level (32). If volume expansion is not sufficient, a carefully titrated infusion of dopamine can be used. Hypotension that is resistant to these measures can be treated with 5 to 10 mg of tolazoline intravenously every 30 minutes as needed.

Minoxidil

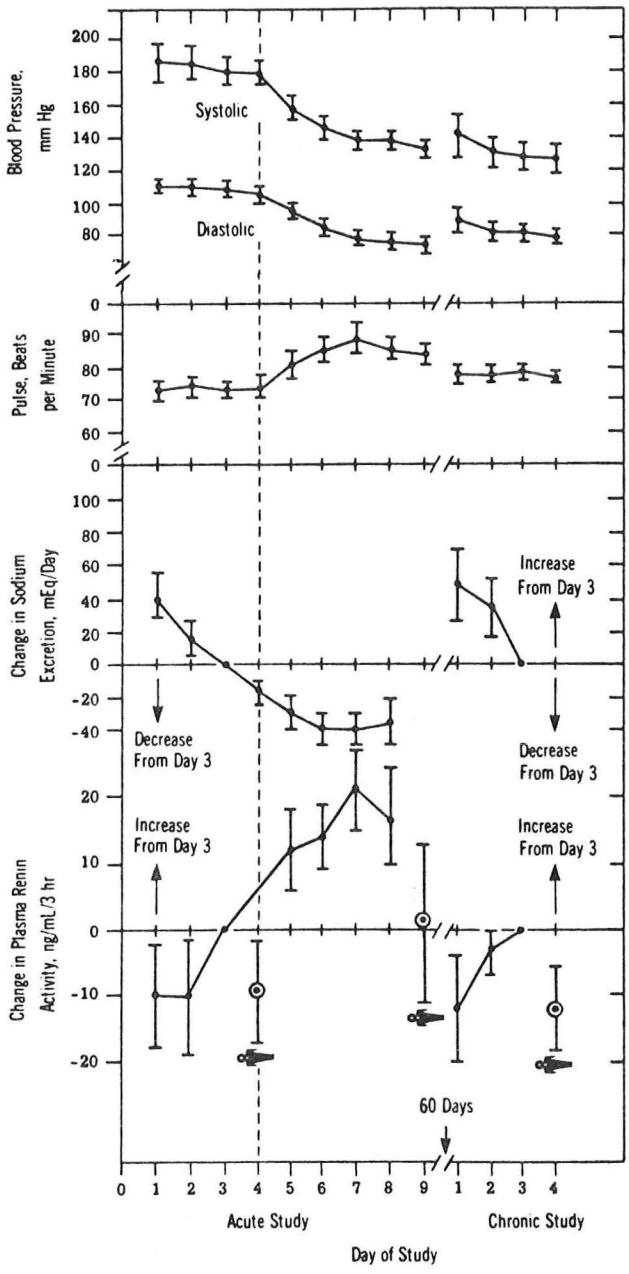
Minoxidil is a potent, direct acting arterial vasodilator that has been used to treat severe drug resistant hypertension. When taken orally, it is rapidly absorbed from the gastrointestinal tract and blood concentrations peak within one hour (33). It has a plasma half-life of about 4 hours but its antihypertensive effect is much longer (greater than 24 hours). It is cleared by the liver making it an acceptable drug for use in patients with renal failure.

Its potency as an antihypertensive agent has lead to its use in the treatment of patients with severe hypertension that is resistant to conventional drug therapy. Many studies, such as that by Bryan, et al. (34), have demonstrated that it is very effective in controlling the hypertension of such patients and is safe if patients are monitored carefully.

EFFICACY OF ORAL MINOXIDIL IN HYPERTENSIVE URGENCIES

In 1979, Grim and coworkers (35) described a regimen utilizing minoxidil to rapidly control the severe hypertension of 12 patients who were already taking a diuretic (hydrochlorothiazide or furosemide) and propranolol (160 mg to 320 mg/day). The regimen started with an oral dose of 1 mg of minoxidil, and the dose was increased by 1 mg every six hours until the goal blood pressure of 140/90 mm Hg was reached. The blood pressure response, heart rate, sodium excretion on a fixed sodium diet (90 meq/day) and plasma renin activity can be found in Figure 13. With this regimen, blood pressure fell gradually and smoothly over several days. No patient required more than 40 mg of minoxidil per day and no serious side effects were noted. Sodium excretion fell and plasma volume increased by a mean of 783 mL despite diuretic therapy. Plasma renin activity increased in all patients including one with primary hyperaldosteronism.

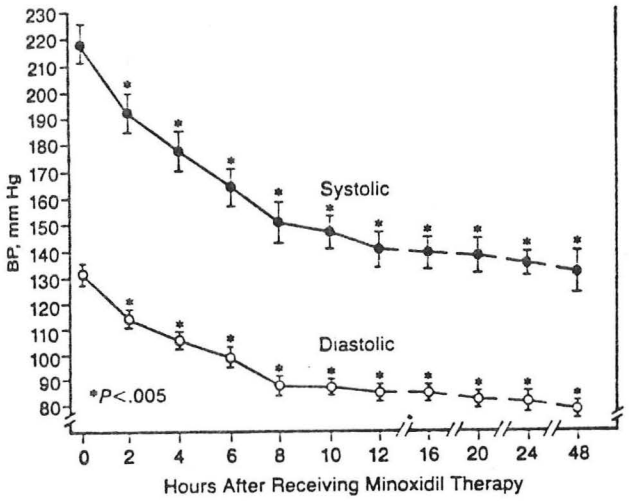
Figure 13



In 1980, Bauer and Alport (36) were the first to report a method of using minoxidil to lower blood pressure over several hours instead of days. In a later study by the same group (37), patients with severe hypertension in need of rapid hypotensive therapy were given initially 40 mg of oral propranolol and 40 mg

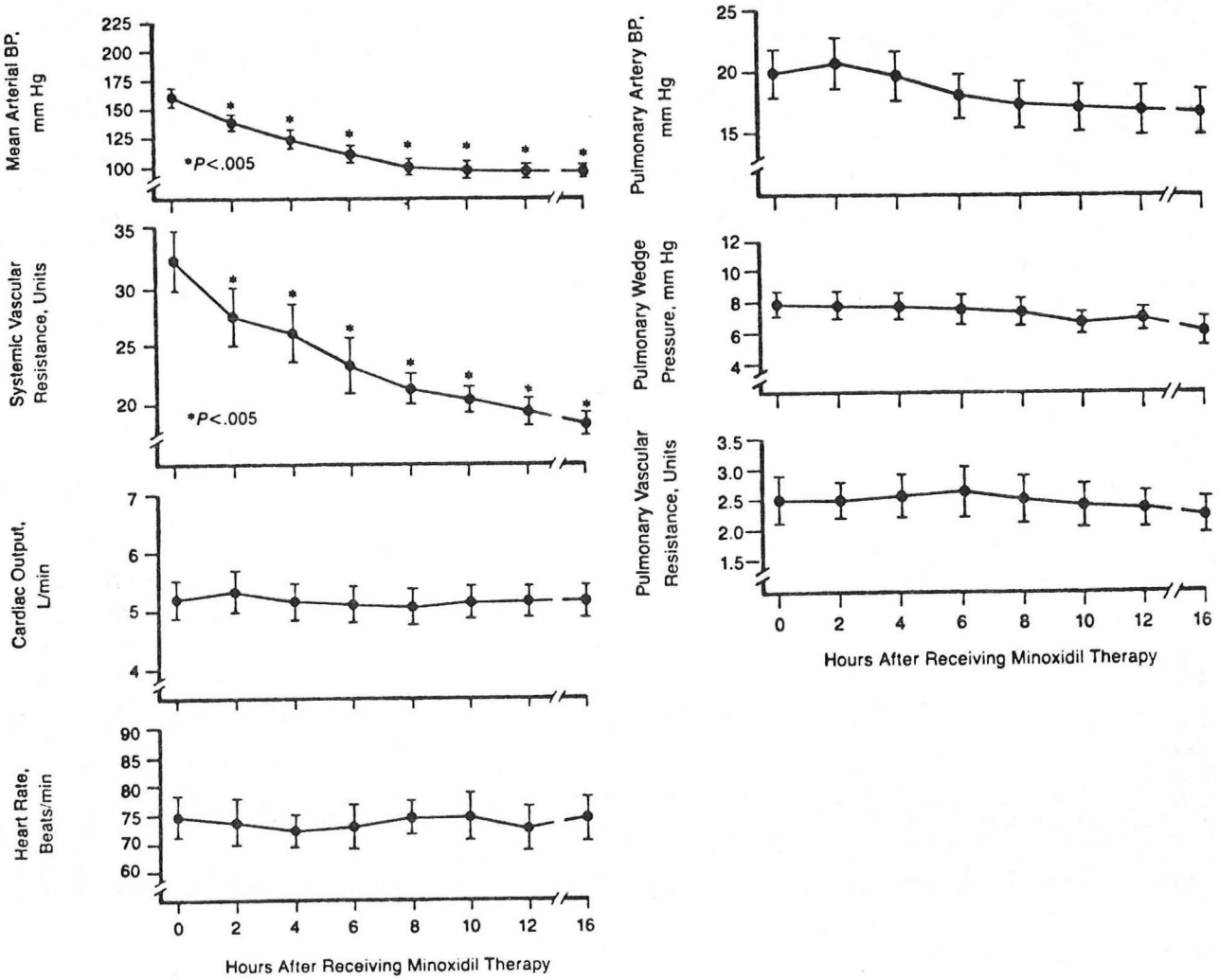
of oral furosemide followed in 2 hours by 20 mg of oral minoxidil if the diastolic blood pressure was 120 mm Hg or more. If necessary, patients were then given an additional dose of minoxidil in four hours to lower the diastolic pressure to a predefined goal of 100 mm Hg at four hours and 90 mm Hg at 8 to 12 hours. The size of this second dose was estimated from the patient's response to the first minoxidil dose. The blood pressure response to this regimen is shown in Figure 14.

Figure 14



Mean diastolic blood pressure, which was 130 mm Hg at the time the patients received the first dose of minoxidil, fell to 105 mm Hg at 4 hours. Because the goal diastolic pressure of 100 mm Hg had not been met, eight of the nine patients in this study received an additional dose of minoxidil. Mean diastolic blood pressure fell to 89 mm Hg by 8 hours and 86 mm Hg by 12 hours. No episodes of hypotension occurred during the study (defined as a blood pressure of less than 110/60 mm Hg). Other hemodynamic parameters that were monitored can be found in Figure 15. Mean arterial pressure fell due to a dramatic fall in total peripheral resistance. No significant change was detected in cardiac output, heart rate or pulmonary wedge pressure, probably due to the pretreatment with the diuretic and beta-blocker.

Figure 15



In summary, minoxidil is effective in acutely lowering blood pressure in selected patients. Sympathetic blockade with a beta blocker and pretreatment with a diuretic are necessary to counteract the cardiac stimulating and water retaining properties of this drug. In treating hypertensive urgencies, it is most useful in patients who have previously taken the drug and in patients who can tolerate acute beta blockade. As with other potent arterial vasodilators, it should not be used in patients with coronary artery disease.

SIDE EFFECTS OF ORAL MINOXIDIL TREATMENT

Minoxidil has several side effects which must be considered when using the drug to treat hypertensive urgencies. Because of its potent vasodilating properties, the drug activates the sympathetic nervous system causing reflex tachycardia and an increase in cardiac output. This can result in an increase in myocardial oxygen demand precipitating angina pectoris or even myocardial infarction in patients with coronary artery disease. Sympathetic activation also results in an increase in plasma renin activity in many patients. These side effects can usually be controlled with appropriate doses of a beta-blocker. Reversible T-wave changes may occur with minoxidil. These are most often seen acutely (within the first week) and may occur without other evidence of myocardial damage. Pericardial effusions occasionally occur in patients receiving minoxidil for chronic antihypertensive therapy, especially those who retain significant sodium and are predisposed to the development of pericardial effusions, e.g., patients with renal failure. Hypotension can occur and may last for several hours or even days (38). Sodium and water retention usually occurs when minoxidil is used acutely to lower blood pressure. Consequently, diuretics are almost always required.

LABETALOL

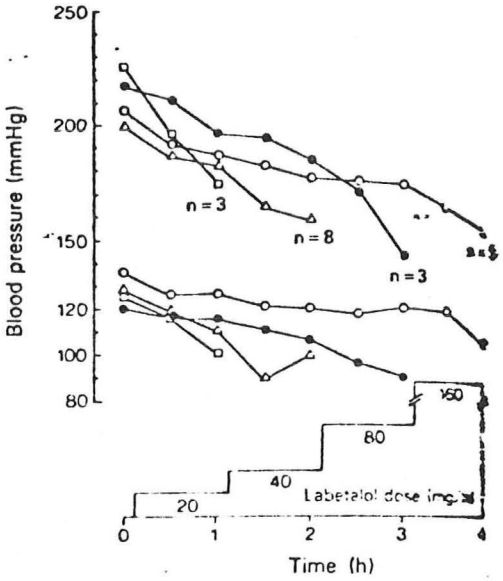
Labetalol is a relatively new antihypertensive agent with a mechanism of action that combines both alpha and beta adrenoreceptor blockade. It is a effective agent that controls hypertension comparable to other step 2 and 3 drugs (39,40). Unlike most other beta blocking drugs, it significantly lowers total peripheral resistance as part of its antihypertensive action, and it does not depress cardiac output (41). Labetalol is available in both oral and intravenous forms. The ratio of beta to alpha blockade is approximately 3:1 for the oral form and 7:1 for the intravenous form of the drug (42).

EFFICACY OF LABETALOL IN HYPERTENSIVE EMERGENCIES AND URGENCIES

Labetalol has been used in both hypertensive emergencies and urgencies with most studies using the intravenous form. The drug has been available for several years in Europe. Most investigators have found the drug to provide rapid blood pressure reduction with an acceptable side effect profile.

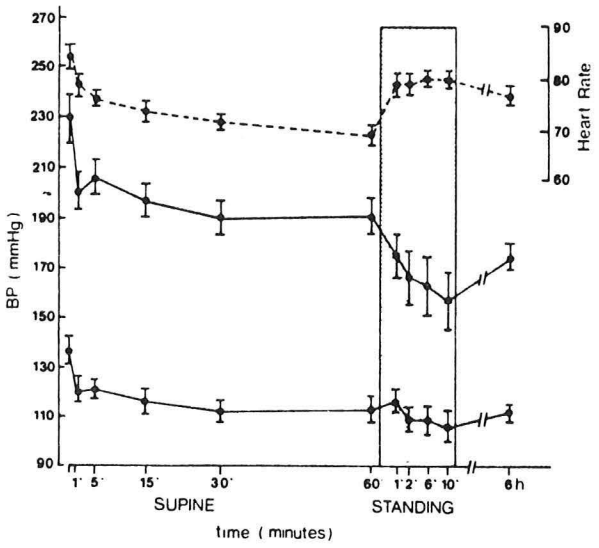
Cummings, et al. (43), gave incremental infusions of labetalol to nineteen severely hypertensive patients. The drug was given by continuous intravenous infusion at 20, 40, 80 and 160 mg/hr starting at 20 mg/hr and increasing to the next higher dose every hour until an adequate blood pressure response was obtained. The blood pressure response of these patients is shown in Figure 16. The patients are divided into four groups depending on the maximum dose of labetalol given.

Figure 16



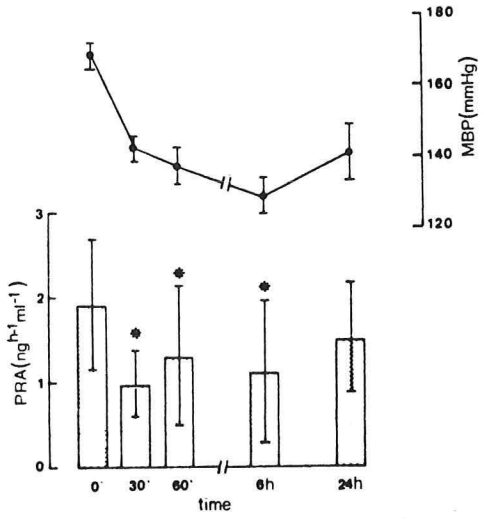
Labetalol can also be given by bolus therapy. Lechi,et al. (44), found that the administration of 1 mg/kg of labetalol injected over three minutes produced a significant fall in systolic and diastolic blood pressure over 5 minutes. The reduction in blood pressure reached a maximum in 6 hours. No serious side effects were noted although a significant orthostatic drop in blood pressure was demonstrated (Figure 17). Plasma renin activity decreased slightly in these patients after the injection of the drug (Figure 18).

Figure 17



Blood pressure and heart rate after a single rapid injection of labetalol (1 mg/kg over 3 min). After 3 h, the patients were kept for 10 min in erect position (stippled area).

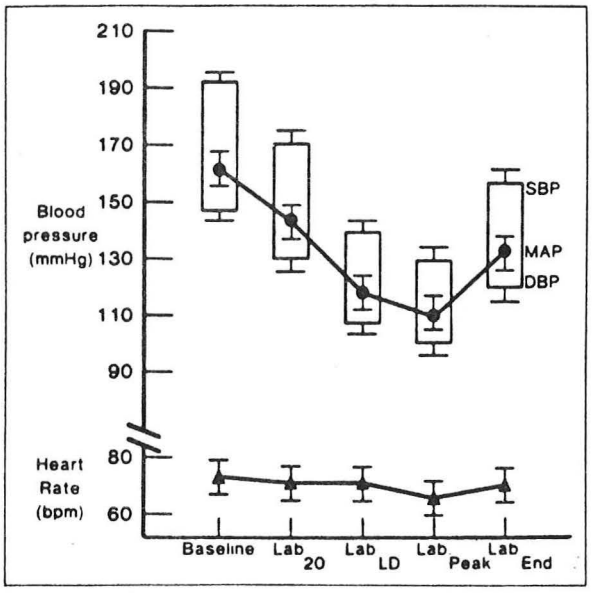
Figure 18



Mean blood pressure and plasma renin activity after a single dose of labetalol (rapid injection, 1 mg/kg over 3 min).

In 1983, a multicenter study (45) was published from the United States that examined the safety and efficacy of intravenous labetalol in the treatment of severe hypertension and hypertensive emergencies. A 20 mg bolus of labetalol was given over 2 minutes to patients with a supine diastolic blood pressure of 125 mm Hg or greater and/or a supine systolic blood pressure of 200 mm Hg or greater. Additional doses of 40 to 80 mg of labetalol then were given at 10 minute intervals until the goal blood pressure was reached or a maximum cumulative dose of 300 mg had been given. Supine blood pressure fell significantly in these 59 patients from 204/134 mm Hg to 139/93 mm Hg in those previously untreated for hypertension and 216/134 mm Hg to 146/94 mm Hg in those already receiving antihypertensive therapy. The response of all 59 patients is shown in Figure 19.

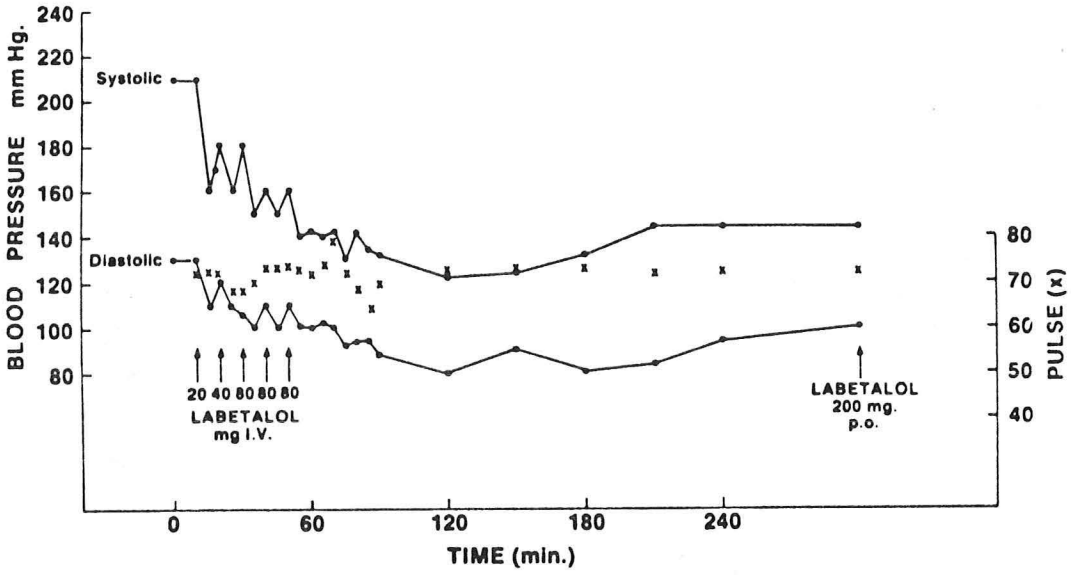
Figure 19



Supine systolic blood pressure (SBP), diastolic blood pressure (DBP) mean arterial blood pressure (MAP), and heart rate (HR) at baseline, after the first 20 mg mini-bolus of labetalol (lab_{20}), after the last dose of labetalol (lab_{LD}), the lowest blood pressures recorded after the last injection (lab_{PEAK}), and the blood pressures and heart rate just prior to initiation of oral labetalol (lab_{END}) for the total study population (n = 59).

Figure 20 illustrates a typical treatment course of a patient with a blood pressure of 209/130 mm Hg who was treated with intravenous labetalol. With incremental boli of labetalol (arrows), blood pressure smoothly declined to the 130-140/80-90 mm Hg range. After 4 hours when the blood pressure had begun to rise, oral labetalol was given (46).

Figure 20

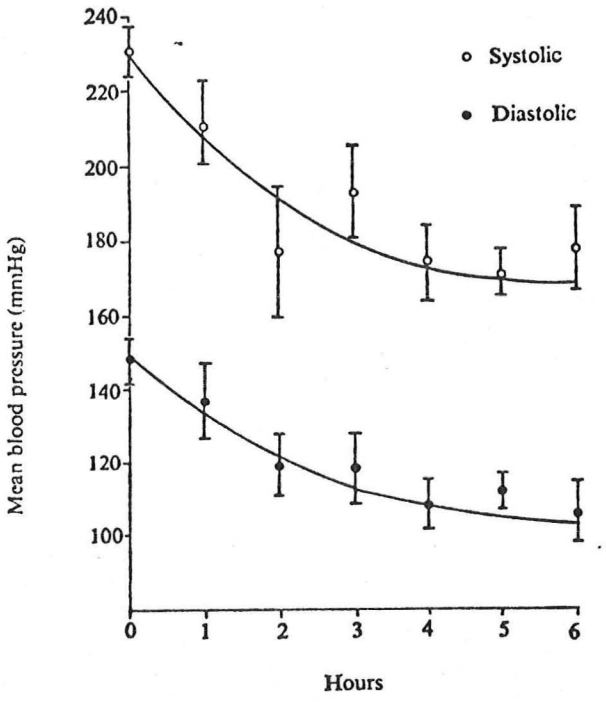


The use of labetalol in the treatment of hypertension that is complicated by the presence of myocardial infarction has been studied by several groups over the past few years. In general, it has been found to be effective in lowering blood pressure without serious side effects in this setting (47,48,49). Labetalol has been found to be very effective in reducing systemic blood pressure with little effect on pulmonary wedge pressure in patients who initially have normal left ventricular filling pressures. In patients with an elevated wedge pressure who have an acute myocardial infarction and hypertension, the drug lowers the systemic blood pressure while reducing left ventricular preload significantly (47).

Oral labetalol has been used to treat severe hypertension in doses of 100 mg to 400 mg. Ghose and Sampson (50) reported such a study where a gradual decline in systolic and diastolic blood pressure was seen after patients with diastolic blood pressures

exceeding 130 mm Hg were given doses of labetalol between 200 mg and 400 mg. The hypotensive response of nine patients is shown in Figure 21.

Figure 21



SIDE EFFECTS OF LABETALOL

Because of its beta blocking effects, labetalol should not be given to patients with asthma, sinus bradycardia, atrioventricular block greater than first degree, patients with right sided heart failure or left ventricular failure with a low cardiac output. The incidence of side effects with acute and/or chronic therapy with labetalol is similar to other antihypertensive agents and serious side effects are unusual if patients who are to receive the drug are carefully selected. Common side effects are nasal congestion, postural symptoms, sleep disturbances, sedation, gastrointestinal symptoms, dry mouth and impotence. Paresthesias (especially involving the scalp), headache, weakness and edema are also seen.

Nifedipine

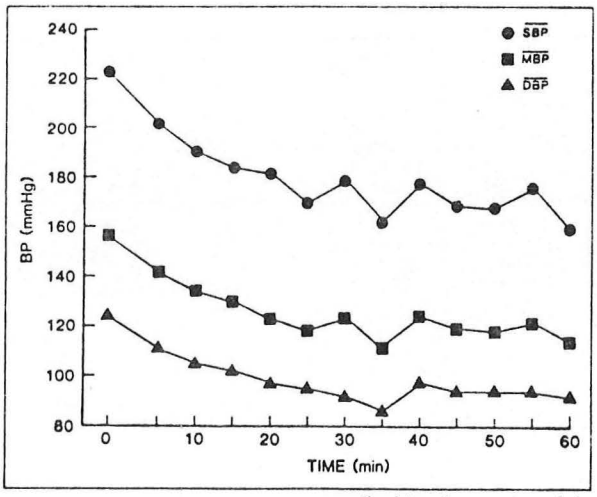
Nifedipine is a calcium channel blocker that despite not being approved for use in hypertension has been used extensively for the treatment of hypertensive urgencies and emergencies. It is rapidly absorbed from the oral mucous membranes and gastrointestinal tract and once absorbed has an antihypertensive action that becomes evident within minutes. Nifedipine produces a prompt, predictable fall in blood pressure after sublingual or oral ingestion, and its antihypertensive action lasts 2 to 6 hours. Nifedipine lowers blood pressure by decreasing peripheral vascular resistance while cardiac output, stroke volume, heart rate, cerebral (31) and renal blood flow, plasma renin activity and catecholamines increase .

Nifedipine has several characteristics that make it attractive for use in the treatment of hypertensive emergencies and urgencies. Blood pressure is lowered quickly and hypotension is unusual if the drug is used alone. Angina pectoris and myocardial infarction are unusual after its use because of a favorable balance of myocardial oxygen supply and demand induced by the drug in hypertensive patients. Blood pressure can be lowered quickly without the necessity for invasive hemodynamic monitoring.

EFFICACY OF NIFEDIPINE IN THE ACUTE TREATMENT OF HYPERTENSION

In 1976, Aoki and coworkers (51) treated 19 patients with hypertensive emergencies with 30 mg of sublingual nifedipine. Mean arterial pressure was reduced 28% within 15 minutes in these patients, and the effect of the drug lasted for 4 hours. Since that time multiple other studies have documented the efficacy of nifedipine in acutely treating severe hypertension (31,52,53,54,55,56,57,58,59,60). Figure 22 illustrates the typical blood pressure response of 30 patients with hypertensive emergencies to 10 mg or 20 mg of sublingual nifedipine (58).

Figure 22



Nifedipine has been used successfully in treating severe hypertension in patients suffering from a variety of hypertensive complications. Given, et al.(57), used the drug in nine patients with severe hypertension and congestive heart failure with preserved left ventricular function as assessed by echocardiography. A dose of 10 or 20 mg of nifedipine was given to these patients resulting in a subsequent fall in blood pressure from 211/105 mm Hg to 153/78 mm Hg. No adverse reactions were noted and long term therapy with the drug resulted in good blood pressure control and symptomatic improvement of congestive failure in the patients. Others have used nifedipine in patients with congestive heart failure with similar results (55).

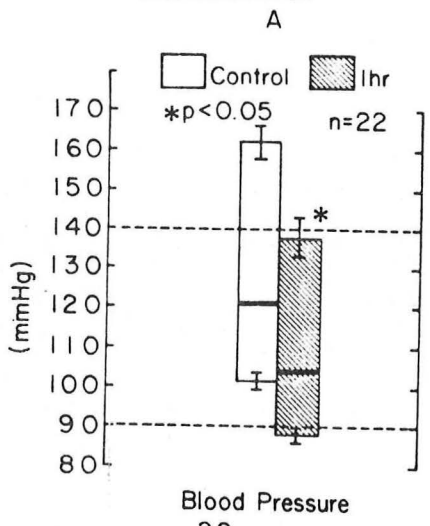
SIDE EFFECTS OF NIFEDIPINE

Serious side effects with nifedipine are uncommon. Headache, flushing, palpitations with chest pain and gastrointestinal symptoms (diarrhea) may occur. Hypotension is unusual but may occur and may be associated with the appearance or worsening of angina pectoris, primarily in patients receiving beta blockers or nitrates (61). Care should be exercised when nifedipine is given to patients with hypertensive encephalopathy since the increase in cerebral blood could theoretically worsen cerebral edema.

Angiotensin converting enzyme inhibitors

Although the role of the renin-angiotensin system in the pathogenesis of hypertension remains controversial, suppression of this system results in blood pressure reduction in many hypertensive patients. Captopril is a well tolerated, effective agent used for many years for the treatment of hypertension. Early studies on the effectiveness of captopril, such as that by Johns, et al.(62), demonstrated an acute blood pressure lowering effect of captopril within 1 hour of an effective dose (Figure 23).

Figure 23

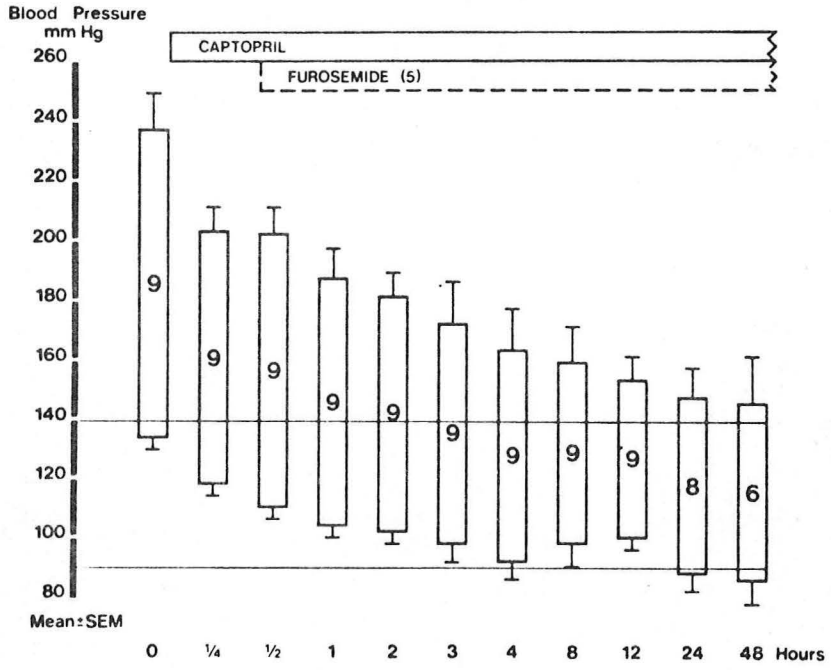


EFFICACY OF ACE INHIBITORS IN HYPERTENSIVE EMERGENCIES

Case and coworkers (63) demonstrated the effectiveness of captopril by treating 20 patients with severe and malignant hypertension, some of which had encephalopathy. In this study, a single dose of 10 to 50 mg of captopril was given in the acute phase. A hypotensive effect was noted within 15 minutes and reach a maximum after 90 minutes. Mean arterial pressure fell from 132 mm Hg to 107 mm Hg without a significant change in heart rate. Two of these patients were receiving nitroprusside at the start of the study, and each was able to be withdrawn from this drug within 30 minutes of starting captopril. In addition, four patients who had hypertensive encephalopathy had rapid resolution of symptoms after captopril was started.

In a similar study, Biollaz (64) examined the use of captopril in 9 untreated hypertensive patients with evidence of neurologic or cardiac decompensation. Patients were given 25 mg of captopril and within 30 minutes blood pressure had decreased from 239/134 mm Hg to 204/118 mm Hg (Figure 24). Thereafter, captopril was continued at a dose of 200 to 300 mg/day. Five patients required furosemide to obtain effective control.

Figure 24



Enalapril has been reported to be useful in the treatment of malignant hypertension in patients with systemic sclerosis who were intolerant to captopril (65). Finally, enalaprilat, the parent compound of enalapril, has been given intravenously to 11 patient with accelerated hypertension (66) with encouraging results. Obviously, more studies are needed before recommendations can be made regarding these two drugs.

SIDE EFFECTS

The most serious side effects of captopril are neutropenia and proteinuria, but these occur only after weeks of therapy. Hypotension can occur especially in patients who are volume depleted from diuretic therapy or other causes.

CONCLUSION

A summary of the dosing schedules and side effects of the most useful drugs now available for the treatment of hypertensive urgencies can be found in the accompanying table. For most real hypertensive emergencies, therapy should be undertaken with one of the traditional drugs used for treating these conditions (nitroprusside, trimethaphan or diazoxide). Labetalol, hydralazine and nifedipine can be used in some of these situations if patients are carefully chosen. Treatment of a hypertensive urgency, on the other hand, usually does not require the rapid, aggressive reduction in blood pressure that is obtained with the parenteral drugs. In these cases, blood pressure can be lowered over several hours by one of the oral loading techniques described above to avoid the risk of hypotension and the discomfort of intravenous infusion. Patients can then be started on a suitable regimen, preferably with the drug used for the acute treatment, with long term control as a goal. One should not forget that a major part of the emergency department treatment of hypertension involves finding the reasons why a patient has lost control of his/her blood pressure. Correcting factors that favor noncompliance, the primary reason for loss of hypertension control in most patients, is just as important as the acute treatment of hypertension in most patients.

TABLE: NEW DRUGS USED IN HYPERTENSIVE URGENCIES

DRUG	DOSE	SIDE EFFECTS
Prazosin	1-5 mg	Hypotension(orthostatic) Dizziness, Headache, Weakness, Drowsiness
Clonidine	0.1-0.2 mg initially followed by 0.1 mg q 1 hr to maximum of 0.7 or 0.8 mg.	Sedation, Dizziness, Bradycardia, Orthostasis, Dry Mouth
Minoxidil	10-20 mg orally, 2 hours after beta blockade with oral propranolol 40 mg, and furosemide 40 mg	Tachycardia, Salt Retention, Angina Pectoris
Labetalol	200-400 mg orally 20 mg intravenously over 2 minutes. Addition injections of 40 or 80 mg can be given at 10 min intervals to total of 300 mg or Continuous infusion starting at 20 mg/h and titrate blood pressure to desired level.	Dizziness, Paresthesias, Nausea, Vomiting, Hypotension
Nifedipine	10 -20 mg orally or sublingually May be repeated in 30 min. if adequate response not obtained	Hypotension, Headache, Angina, Edema, Tachycardia
Captopril	25 mg initially followed by furosemide if needed	Hypotension (especially if already on diuretic), neutropenia, proteinuria

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