SUMMARY  Malignant hypertension still constitutes a medical emergency, particularly when com-
plicated by renal failure, encephalopathy, or left ventricular failure. A shift to the right of the
autoregulatory curve of cerebral blood flow (and probably of renal blood flow) is known to occur in
patients with hypertension. Local cerebral edema, complicating the malignant phase, is likely to
aggravate this trend. While inadequate or tardy treatment leads to encephalopathy, renal and cardiac
failure, overaggressive treatment may also result in damage to brain, heart, and kidney. Recent
reports of neurological damage, sometimes fatal, following aggressive hypotensive treatment suggests
the need for a reappraisal of current practices. More investigation is needed to determine the effects of
the various classes of antihypertensive drugs on organ perfusion, particularly of brain, heart, and
kidney, in both normal and hypertensive humans. Other hypertensive crises include raised arterial
pressure in association with acute dissection of the aorta and in the presence of stroke or subarachnoid
hemorrhage. While there is agreement about the need for urgent hypotensive treatment in patients
with aortic dissection, there is no information with which to base rational decisions in the manage-
ment of high arterial pressure in the acute phase of stroke or subarachnoid hemorrhage.
and long term. Overrapid and overfar reduction of pressure before fibrinoid has been reversed will lead to reduced perfusion, but uncontrolled hypertension prevents healing and allows further ischemic damage.

Renal Function and Malignant Hypertension

The management of malignant hypertension has changed over the last 30 years. Because renal failure was the major cause of morbidity or death in untreated or partially treated cases, the performance of the kidneys in response to treatment has tended to dominate practice. Before the advent of renal units and renal replacement therapy, acute loss of renal function resulting from rapid lowering of arterial pressure was commonly fatal. In the presence of a blood urea concentration exceeding 60 mg/100 ml (BUN over 30 mg/100 ml; blood urea over 10 mmol/liter), it was once recommended that pressures be lowered only with great caution; indeed, if the urea concentration rose further on treatment, it was suggested that not only should antihypertensive treatment be stopped but that the use of vasopressor drugs such as norepinephrine should be considered. This overly conservative approach was changed radically when it became apparent that the renal failure induced by aggressive treatment could be managed successfully by regular hemo or peritoneal dialysis. It was then generally recommended that arterial pressure be reduced to "normal levels" by diazoxide with or without furosemide, and Pickering at one time advocated the urgent use of intravenous diazoxide to be followed by furosemide, allowing up to 1 g of diazoxide and 100 mg of furosemide in the first 24 hours of treatment. The early response to this aggressive approach has commonly been a fall in glomerular filtration and a resultant rise in blood urea and creatinine concentrations, and, on occasion, in the most advanced cases, oliguric renal failure. In many patients, this further loss of renal function is transient, but it may be prolonged or permanent. Despite reports of a delayed improvement of renal function in such cases, presumably as a result of healing of fibrinoid lesions, recovery is rarely more than partial.

Despite these ill-effects, survival figures resulting from this change of practice (now 80% at 5 years) were so much improved from previous experience (death within 6 to 12 months) that the aggressive approach using parenteral drugs has not been questioned until recently. However, as long ago as 1954, Finnerty et al. drew attention to the marked differences in cerebral blood flow in relation to arterial pressure in normotensive and various hypertensive states. When hypotension was induced by head-up tilt during infusions of hexamethonium, the threshold of cerebral ischemia was observed at mean pressures as low as 29-35 mm Hg in normals, 45-50 mm Hg in those with essential hypertension, and at 90 mm Hg in those with malignant hypertension.

Cerebral Perfusion in Malignant Hypertension

Cerebral blood flow is normally autoregulated to allow normal perfusion at mean arterial pressures of between 60 and 160 mm Hg. In chronic hypertension, the autoregulatory curve is shifted to the right, presumably because of structural changes that have occurred in small arterioles in response to raised pressure. Strandgaard et al. suggested a lower limit on the curve, at a mean pressure of 120 mm Hg, but despite these suggestions, the possibility that immediate reduction of arterial pressure to "normal" levels might on occasion cause neurological damage was until recently discounted. A number of publications, however, have now drawn attention to the risks of cerebral ischemia and infarction precipitated by aggressive antihypertensive treatment. The cerebral lesions revealed at autopsy in fatal cases resembled very closely those produced by extreme hypotension in experimental animals and in humans. The proper approach to the management of malignant hypertension would seem, then, to be to steer between inadequate treatment on the one hand, which would probably result in the further development of fibrinoid necrosis or at least would prevent healing, and overrapid reduction on the other hand, resulting at worst in cerebral infarction, myocardial ischemia, and partially recoverable ischemic acute tubular necrosis. In the absence of accurate noninvasive methods with which to follow cerebral and renal blood flow during treatment, the approach is necessarily empirical. The difficulties are not helped by our very incomplete knowledge of the effects of the various classes of antihypertensive drugs on organ perfusion at different arterial pressures.

Uncomplicated Malignant Hypertension

Patients with accelerated hypertension uncomplicated by renal failure, left ventricular failure, or encephalopathy should be admitted to the hospital as soon as possible, with close attention paid to renal function for the first 5 to 10 days of treatment. There is no evidence of the need for parenteral treatment with drugs such as nitroprusside, diazoxide, trimethaphan, or labetolol. Oral agents, such as beta-adrenergic blocking drugs combined with a diuretic and, if necessary, a vasodilator, are perfectly satisfactory. Nadolol is a logical choice of a beta-adrenergic blocker since it has been shown to preserve renal blood flow in contrast to other drugs of its class. In the light of current knowledge of the shift to the right of the autoregulatory curve of cerebral (and probably renal) perfusion, it is probably unwise to attempt full control in the first week of treatment. To what level the pressures should be reduced initially is a matter of guesswork; a reasonable figure might be 160/110 mm Hg for the first 48 hours and perhaps 150/100 mm Hg in the succeeding few days. Much depends on the clinical response in the individual patient. There is evidence that malignant hypertension is frequently of renovascular origin and, thus, full investigation is justified in most cases.

Malignant Hypertension and Renal Failure

When malignant hypertension is accompanied by renal failure, it is often not possible to be sure whether...
renal dysfunction is primary (e.g., glomerulonephritis) or secondary to malignant nephrosclerosis. Whenever is the case, the need to lower arterial pressure quickly to promote healing of fibrinoid lesions in arterioles is more urgent than in the uncomplicated case of malignant hypertension. Again, the patient should be admitted to hospital urgently, preferably to an intensive care unit. How fast and how far to lower the arterial pressure is again a matter of debate, since overaggressive treatment may cause neurological ischemic damage and probably does cause some degree of acute tubular necrosis from which recovery is never complete. Whether a less aggressive approach than has been the practice in recent years would or would not result in a lesser initial rise of plasma urea and creatinine and ultimately a better rather than a worse GFR is unknown. No control data are available and none are likely to become so. It is the practice in Oxford to use a parenteral labetalol infusion for the first 24 hours, according to the protocol of Cumming et al. This provides a smooth, controlled fall in arterial pressure without tachycardia or activation of the renin-angiotensin system. Oral therapy is then given, aiming at pressures in uncomplicated cases of around 160/100 mm Hg for the first 48 hours and then 150/100 mm Hg during the first week of treatment. Vasodilators promote salt and water retention, which is a potential cause of failure to control arterial pressure in late and end-stage renal failure when arterial pressure is remarkably dependent on sodium balance. Diuretics are therefore usually required, and only loop agents are effective at a very low glomerular filtration rate (GFR). Captopril has been used in the treatment of hypertensive emergencies, but in rare cases of bilateral renal artery stenosis or stenosis of the artery supplying a solitary kidney, inhibition of converting enzyme whether by captopril or enalapril may result in an abrupt fall in GFR. It would appear that at critically low renal perfusion pressures, an intact renin-angiotensin system may be crucial to autoregulation of GFR.

Hypertensive Encephalopathy

Arterial pressures that exceed the upper limit of autoregulation result in an increase in cerebral blood flow which is more marked in gray than in white matter. This overperfusion damages small vessels and leads to multiple areas of edema, mostly in the cortex. The resultant splitting of vessels by edema within the rigid cranium probably adds to the impairment of autoregulation, making flow particularly pressure-dependent in these edematous areas.

The clinical picture of headache, nausea, and vomiting, which may progress to confusion, focal neurological signs, and fits is alarming. It constitutes the gravest emergency of all the hypertensive crises; untreated, it leads to coma and death. What drug is best to use in this critical situation? Most would advocate sodium nitroprusside as the drug of choice, monitored by an indwelling arterial line. The action of this drug is almost immediate, and excessive falls of arterial pressure are rapidly corrected by headdown tilt and slowing or stopping of the infusion. Most data concerning the effects of nitroprusside on cerebral perfusion derive from investigations of its use in anesthetised patients, and suggest preservation of cerebral perfusion at very low arterial pressures. But this favorable characteristic does not appear to be present in normal conscious humans, in whom Henriksen and Paulson have recently shown falls in mean cerebral blood flow and increases in arteriovenous oxygen differences at mean arterial pressures of 80–90 mm Hg. Decreased cerebral blood flow in response to falls in arterial pressure induced by nitroprusside or trimethaphan have also been reported in normal Rhesus monkeys. Little is known of the effects of other antihypertensive drugs on cerebral perfusion, particularly in patients with malignant hypertension. Hydralazine does not appear to alter flow in normal humans, but in neurosurgical patients it may increase intracranial pressure and thus threaten autoregulation. Diazoxide, given by bolus injection to 10 patients with severe hypertension but without encephalopathy, had little initial effect on cerebral blood flow but 4 hours later blood flow began to fall; it fell in all five patients who required a second injection of diazoxide. Intravenous labetalol appears to reduce cerebral blood flow less than does diazoxide in patients with uncomplicated “benign” hypertension, but its effects in the malignant phase are unknown. Bertel et al. have recently reported the use of nifedipine in oral doses of 10–20 mg in 25 patients with various forms of hypertensive emergency (nine with malignant hypertension, six of whom had encephalopathy). Measurements of total cerebral blood flow before and after nifedipine showed an increase in perfusion in four of five patients, but a fall in three of four patients given intravenous clonidine.

Whatever drug is selected for use in the emergency treatment of encephalopathy, very close observation of neurological status, arterial pressure, and renal function is essential. Again, the Oxford practice is to infuse labetalol, aiming at the same levels of pressure as described in the management of hypertensive crises without encephalopathy. Whatever drug is used, pressure may on occasion fall too far. Elevations of the foot of the bed by 30° will then allow pressure to increase by increasing venous return. Volume replacement is seldom advisable and pressor agents are contraindicated, since they are likely to raise arterial pressure only at the expense of perfusion of vital organs. If neurological signs progress as pressure falls, there may be a case for giving dexamethasone to treat putative cerebral edema, but the evidence is not good.

Malignant Hypertension and Left Ventricular Failure

Loop diuretics given intravenously are remarkably efficacious in the treatment of left ventricular failure. The ideal drug with which to supplement their use will reduce afterload without promoting too much in the way of renal salt and water retention or tachycardia. While nitroprusside has had its advocates, there is a strong case for considering captopril in this situation. It
has remarkable acute effects on left ventricular function in the absence of fluid retention and tachycardia. Since renin activity is high in accelerated hypertension, it is wise to start with a small dose (e.g., 6.25 mg) to avoid an excessive initial fall in arterial pressure.

**Hypertension and Dissecting Aneurysm**

The results of surgical management of acute dissection of the ascending aorta are better than those of medical management, but for acute lesions of the descending aorta, medical management appears equally good. A prime consideration in both cases is the need to lower arterial pressure urgently, ideally with a drug that does not cause tachycardia. Traditionally, trimethaphan infusion has been advocated because, unlike nitroprusside or diazoxide, it decreases the rate of rise of arterial pressure with each beat. Variable elevation of the head of the bed should be used with this very short-acting ganglion-blocking drug. The aim is to reduce systolic pressures to 100 mm Hg by an infusion dose ranging from 1 to a maximum of 15 mg/min. The ill effects of ganglion-blockade (dry mouth, blurred vision, urinary retention, and ileus) make it inappropriate to use this drug for more than 24–48 hours. After the initial control of systolic pressure, therefore, oral agents such as propanolol, methyldopa, guanethidine, or captopril should be given to maintain low systolic pressures and heart rate.

**Hypertension and Acute Stroke**

A major determinant of survival after a stroke is the antecedent systolic blood pressure, and there is evidence that control of arterial pressure after recovery from stroke improves prognosis, but there are no useful data to indicate how to manage high arterial pressure in the presence of an acute stroke. The situation is complex because of the uncertain contribution of possible raised intracranial pressure to any rise in arterial pressure. Benefit from reducing pressure in acute stroke has been claimed. In contrast, Britton et al emphasize the hazards of treatment in this situation; six cases are described in which very high arterial pressure was not gained acceptance. It would seem reasonable in this deplorably uncertain situation to lower only the most alarmingly high pressures in the acute phase, and then only with the greatest caution and careful observation of the effects on cerebral function.

**Hypertension in Subarachnoid Hemorrhage**

The problems presented to the physician by a patient in whom subarachnoid hemorrhage is associated with hypertension are similar to those presented when high arterial pressure is associated with an acute stroke, but with the added problem of cerebral arterial spasm. Persistent constriction of major cerebral arteries occurs most commonly for some 7 days after the initial bleed or after the same interval postoperatively. It has a considerable adverse effect on prognosis. The cause(s) of spasm and its ischemic consequences are not known, and effective treatment for prevention or reversal has not been found. Recent suggestions that serotonin release from platelets may contribute are inconclusive.

The prognosis in subarachnoid hemorrhage is materially worse when associated with evidence of preceding hypertension; the mortality is sixfold higher among hypertensives under the age of 50 years than normotensives.

Whether treatment of hypertension after subarachnoid hemorrhage has occurred would improve or worsen prognosis is not known. Raised intracranial pressure and spasm may compromise perfusion further if arterial pressure is lowered acutely, and it is possible that hypertension in this situation is in some measure protective. The results of one multicentre study were taken to support the use of hypotensive therapy in the acute phase, but the study was badly designed and has not gained acceptance. It would seem reasonable in this deplorably uncertain situation to lower only the most alarmingly high pressures in the acute phase, and then only with the greatest caution and careful observation of the effects on cerebral function.

---

**References**


27. Short D: The vascular fault in chronic hypertension, with particular reference to the role of medial hypertrophy. Lancet 1: 1302, 1966


30. Pierach A: Local and relative hypotension as the cause of cerebrovascular accident. In Cerebral Circulation and Stroke, edited by Zulch KJ. Berlin: Springer Verlag, 1971, p 439


55. Goldberg HI, Codardo RA, Banko RS, Reisch M: Patterns of cerebral dysautoregulation in severe hypertension to blood pressure reduction with diazoxide. In Cerebral Function, Metabolism and Circulation, edited by Ingvar DH, Lassen NA. Copenhagen: Munksgaard, 1979, p 64


CRUICKSHANK: You mentioned subarachnoid hemorrhage. I have just recently seen a patient with subarachnoid hemorrhage and I think that it is an interesting concept. You might even alter the pharmacological effect of drugs with barbiturates. If anesthesia, for example, turns nitroprusside into a drug that preserves cerebral blood flow when it doesn't do so normally, barbiturates may well have an effect. Of course, people have used dexamethasone to try to reduce cerebral edema, but there are only anecdotal reports.

DIENSTL: In some cases it is important to protect the brain cortex. Has anybody tried to protect it with barbiturates?

LEDINGHAM: No, I don’t think so. I think that is an interesting concept. You might even alter the pharmacological effect of drugs with barbiturates. If anesthesia, for example, turns nitroprusside into a drug that preserves cerebral blood flow when it doesn’t do so normally, barbiturates may well have an effect. Of course, people have used dexamethasone to try to reduce cerebral edema, but there are only anecdotal reports.

CRIUICKSHANK: You mentioned subarachnoid hemorrhage, and the lack of data. Neil-Dwyer and I have just published in the British Medical Journal a series of 204 cases randomized within 24 hours of the hemorrhage to either oral propranolol, an alpha-blocker, or placebo. The last 100 of the cases had just beta-blocker alone or placebo. There were significantly fewer deaths in the beta-blocker group, and at 1 year follow-up they also had significantly fewer neurological deficits. We measured cerebral blood flow in the first week in a few of the patients, and found that it was decreased by about 5% in those taking the beta-blocker.

LEDINGHAM: Yes, I have in fact just recently seen that paper. I think it is the only piece of information. People are also talking anecdotally about using ketanserin to reverse spasm.

STRANDGAARD: I agree with everything you say, but why did you say on your last illustration “Avoid phenothiazines”? In Scandinavia it is popular to lower severely raised pressures with small intravenous doses of chlorpromazine.

LEDINGHAM: I am glad you raised that point. My point is not a very scientific one, but so often when you are treating the malignant hypertensive crisis, the encephalopathy is associated with a great deal of restlessness, aggressiveness, and cerebral irritation. Patients are often disruptive at night while they are in the intensive care unit, and it is all too common that someone phones from the house officer’s bed “Give him some chlorpromazine” and doesn’t come to see the patient. And the next thing that happens is that there is no arterial pressure, because chlorpromazine plus the other agents is often very hypotensive indeed, and once you do get a hypotensive effect from chlorpromazine it is often quite difficult to get the pressure up again.

MACGREGOR: In thinking of the kidney in malignant hypertension, there are two other factors (besides fibrinoid necrosis) that make renal function worse: the very high level of angiotensin II and the sodium loss that often occurs. Just in terms of the kidney, it would seem more logical to treat patients who have renal impairment and high levels of angiotensin II with sodium and a converting-enzyme inhibitor.

LEDINGHAM: I think that is a very good idea. I am bothered about the ultimate renal function in these patients, and I agree that if you inhibited angiotensin, within the kidney and outside, and restored perfusion, this would be a very effective treatment. The problem is that, in Oxford at least, we are not seeing this condition even in renal units, and the burden of the work has probably got to fall on units that do see it, probably in Africa or South America.

MACGREGOR: There may be differences between Oxford and London. We certainly see malignant hypertension and renal failure. Using this treatment we have had some remarkable improvements in renal function. The cases are anecdotal, and other regimens have also occasionally improved renal function.
Management of hypertensive crises.
J G Ledingham

_Hypertension_. 1983;5:III114
doi: 10.1161/01.HYP.5.5_Pt_2.III114

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1983 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/5/5_Pt_2/III114

 Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Hypertension_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Hypertension_ is online at:
http://hyper.ahajournals.org//subscriptions/