Management of Hypertensive Crises

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SUMMARY Malignant hypertension still constitutes a medical emergency, particularly when complicated 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 management of high arterial pressure in the acute phase of stroke or subarachnoid hemorrhage.

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SITUATIONS in which the need to lower arterial pressure acutely constitute an emergency. These situations are few; chief among them are hypertension in the malignant phase (complicated or not by encephalopathy, renal failure, or left ventricular failure) and hypertension associated with acute dissecting aneurysm of the aorta. Malignant hypertension is now much less common than it was when Kincaid-Smith and her colleagues estimated it to occur in as many as 1% of the hypertensive population, perhaps because of improved methods of detection and treatment of patients with high arterial pressure. Particular difficulties in the treatment of hypertension arise also in the management of patients who have suffered a stroke or subarachnoid hemorrhage.

Accelerated Hypertension: Underlying Considerations

The pathological lesion that characterizes malignant hypertension is fibrinoid necrosis of the arteriolar wall. The lesion comes about as the result of a rise in arterial pressure sufficient to overcome the muscular resistance of small arterioles, leading to "ballooning" of areas of the vessel wall. These dilated areas tend to enlarge and fuse, with resultant damage to endothelial cells. Plasma and its proteins then infiltrate the vascular media, displacing and destroying the smooth muscle cells. Vascular narrowing is then the result of the stripping of endothelium away from the underlying internal elastic lamina, leading to impairment of renal function, cerebrovascular disease, and myocardial disease and failure.

Clinical evidence of fibrinoid change is most obvious in the fundus oculi. Cotton wool spots (which are not exudates, but evidence of retinal infarcts) and superficial flame-shaped hemorrhages with or without papilledema are evidence of the malignant phase. The physical damage to arteriolar walls that underlies this condition is usually the result of very high pressures, but when the rate of rise has been particularly rapid, as may occur in acute nephritis or in preeclampsia or pheochromocytoma, the changes of malignant hypertension may occur in the presence of relatively modest pressures, e.g., as low as 105–110 mm Hg diastolic. The consequence of the vascular lesion is to impair the perfusion of affected organs; if untreated, the kidney bears the brunt of the resultant damage. The fibrinoid necrosis of arteriolar walls impairs the capacity of resistance vessels to autoregulate the blood flow, but animal and clinical studies have shown how reduction of arterial pressure in the malignant phase leads to healing of the arteriolar lesions. This appears to come about by removal of plasma deposits by smooth muscle cells in the media and macrophages in the intima.

These are important observations to consider in choosing an approach to treatment, particularly in relation to perfusion of brain, kidney, and heart in the short
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.22-25 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.26 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.
renal dysfunction is primary (e.g., glomerulonephritis) or secondary to malignant nephrosclerosis. Whichever 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 neurologic 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
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 propranolol, 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 to lower only the most alarmingly high pressures in the acute phase, but the study was badly designed and has not gained acceptance.

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.

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.

References


This page contains references to various sources of information on hypertensive crises, including studies on the effects of hypertension on cerebral function, the management of acute stroke, and the complications of subarachnoid hemorrhage.
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Discussion

Discussants: F. DIENSTL
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J. CRUICKSHANK
S. STRANDGAARD
G. MACGREGOR

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.

CRUICKSHANK: 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 itself, 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.
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