Hypertension and the J-Curve

How low should you go?

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SUMMARY

Recent analyses of treated blood pressure versus events suggest that drug treatment might result in an increase in coronary events or mortality at treated diastolic pressures below 80 mm Hg (the "J-curve"). However, this contention is highly controversial. Both sides of the argument are examined and a balanced approach for target blood pressure goals on treatment is outlined.

RÉSUMÉ

Des analyses récentes portant sur le traitement de l'hypertension artérielle et les accidents pathologiques suggèrent que le traitement médicamenteux pourrait accroître les accidents coronariens ou la mortalité lorsque les tensions diastoliques des patients traités sont inférieures à 80 mm Hg (la "courbe J"). Cette affirmation est toutefois très controversée. L'article examine les deux facettes de l'argumentation et décrit une approche équilibrée pour bien cibler les objectifs du traitement de l'hypertension artérielle.

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DURING THE FIRST HALF OF THE 20th century, little could be done to help people with hypertension. But by the 1960s and 1970s, effective drug therapy to reduce complications was available and proven in clinical trials. Our zeal to treat this condition was reflected in the recommendations of experts to lower diastolic pressure to below 90 mm Hg, or to the lowest possible level achievable without adverse effects.[1] Is this still the correct approach during the 1990s?

Data from insurance studies of untreated patients prove that mortality is proportional to blood pressure level even in the normal range.[2] However, it does not necessarily follow that *treated* blood pressure and mortality have the same relationship. As treated diastolic pressure falls below a critical threshold, mortality (or non-fatal cardiovascular events) might rise. *Figure 1* illustrates the two possible curves in the clinically relevant diastolic pressure range. If there is a critical pressure and the coronary mortality curve resembles a *J* or *U*, care should be taken not to lower pressure too far. This controversy is currently raging in hypertension literature around the world and bears closer scrutiny.

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Does the J-curve exist?

The "J" sayers. The first suggestion that diastolic BP could be lowered too far came about because patients with severe hypertension had an increased incidence of myocardial infarctions with treated pressures less than 105 mm Hg.[3] Data from the Framingham study[4] supported this concept, indicating increased cardiovascular mortality at treated diastolic BP less than 90 mm Hg.

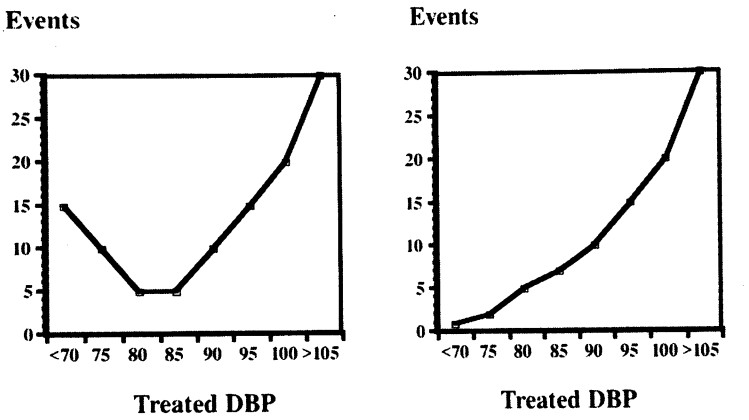
However, it was Cruikshank et al[5] who coined, and became the primary proponents of, the J-curve. They analyzed data from 939 hypertensive patients in the United Kingdom and found an increase in fatal myocardial infarction at treated diastolic BP levels less than 85 mm Hg. This was true for patients with evidence of coronary heart disease (prior infarction, angina, or electrocardiographic changes of ischemia), but not for nonischemic patients (*Figure 2*)[5].

Other studies also support this view. A study of 686 middle-aged hypertensive men in Sweden showed a J-shaped distribution for coronary death or non-fatal infarction versus treated diastolic BP (*Figure 3*)[6]. A similar J-curve is seen in trials of the elderly,[7] both for patients on active treatment and on placebo. The

authors suggest that lower BP levels might simply reflect failing health and are less likely to be related to aggressive drug therapy alone.

Further analysis of 5209 patients in the Framingham cohort[8] compared persons with prior myocardial infarction with those with no existing coronary disease. In the high risk group, both treated and untreated hypertensive patients exhibited a J-curve for death rate versus diastolic BP level. Again, this relationship was not seen among those without coronary disease.

Figure 1. **Schematic depiction of J-curve:** *The chart on the left shows an increase in events below a critical pressure level: the J-curve relationship. The chart on the right shows a continuous positive relationship of diastolic pressure achieved on treatment and events.*



These authors speculate that, for patients with coronary disease, low diastolic pressures are potentially dangerous regardless of treatment status. Cruikshank[9] summarized trials showing the J-curve relationship. These trials indicate a nadir for risk, ie, a J-point, between 80 and 90 mm Hg. This is certainly not an extreme degree of BP reduction and, if true, would force reexamination of our target goals for therapy.

The nay sayers. A meta-analysis, primarily performed by epidemiologists at Oxford, UK, pooled data from 420 000 individuals in nine major prospective observational studies.[10] They found a continuous positive relationship between diastolic BP and coronary heart disease, with no evidence of a J.

The two trials in which patients were randomized to "intensive" therapy[11] versus "usual" therapy[12] showed lower coronary mortality in the intensive groups, who had lower treated blood pressure levels.

In a recent study of systolic hypertension among elderly patients,[13] a J-curve was not observed even though we would expect treated elderly hypertensive patients, with a higher prevalence of underlying coronary disease, to demonstrate the J relationship. Many postmyocardial infarction trials have found less subsequent infarction or death among patients treated with β-blockers even when diastolic pressures were already low. Also, it is conceivable that myocardial infarction leads to a subsequently lower pressure and not the other way around. Finally, all of the studies are retrospective analyses from trials that were not designed for looking at treated pressures. Therefore, there are grounds for denying the existence of the J-curve.

Weighing the evidence. Cruikshank[9] has argued primarily that a J-curve exists only among those with existing coronary disease. The numbers are small for this subset, because most of the larger population trials preselected uncomplicated hypertensive patients for study. More importantly, few patients actually achieve diastolic pressures in the 80 mm Hg range in these studies, and morbid events are even fewer. However, it is impressive that, when we look for a J-curve in a subset with prior coronary disease, it is found more often than not. Most analyses denying the J-curve are in studies in which most patients have no prior coronary disease.

The analysis of these patients would overwhelm any trends seen in the smaller group of those with prior coronary disease (*Figure 3*)[6]. Similarly, in the observational studies of huge populations cited by the Oxford group,[10] most would be of persons without prior coronary disease. Further analysis of the HDFP study,[12] in fact, showed increased mortality in the intensive therapy subgroup with underlying electrocardiogram changes, although as noted above, the overall mortality for the entire intensive care group was less.

Although the J-curve remains controversial, I believe that there is enough evidence to support its existence in treated hypertensive patients with underlying coronary artery disease. However, it is yet unproven whether this is an actual cause-and-effect relationship to antihypertensive therapy, because the J-curve can also be found in placebo groups of some trials. The J relationship could also exist for nonischemic hypertensive patients, but this hypothesis is even more contentious. It is likely, however, on the basis of these trials, that patients with underlying coronary disease are endangered by lower diastolic pressures. Scientific rationale exists for this contention.

Scientific basis

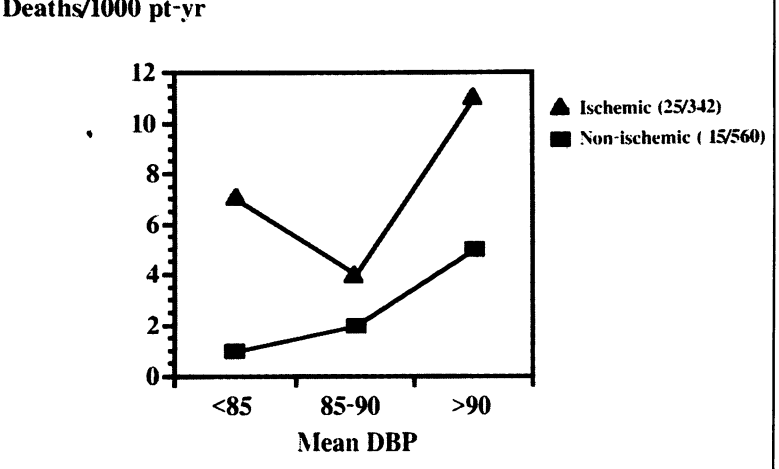
Why might hypertensive patients with coronary disease be especially susceptible to diastolic pressures that are easily tolerated by nonhypertensive patients? First, evidence exists that critical perfusion pressures are needed in certain vascular areas in patients with atherosclerosis. For instance, lowering pressure in stroke patients can lead to neurological symptoms. Further in the cerebral circulation, hypertensive patients are less able to autoregulate blood flow at lower pressures than their normotensive counterparts.[14] Renal blood flow through a stenosed artery can also be compromised at lower pressures. It would not be surprising if this were the case in coronary circulation.

Most coronary blood flow occurs in diastole. (This might explain why no J-curve for coronary events has been found for systolic pressure levels.[9]) Myocardial oxygen extraction is nearly maximal, even at rest. Thus, coronary reserve depends mainly on an increase in diastolic blood flow.

In one study[15] with rapid atrial pacing, hypertensive patients without coronary disease or left ventricular hypertrophy were compared with normotensive control patients. The hypertensive group was less able to increase coronary flow in response to the increased demand of pacing.[15] Poorer response is probably because of increased resistance in the hypertensive patient's coronary vasculature, which would then oppose maximal dilation. The same study showed that hypertensive coronary vessels are more responsive to vasoconstrictor stimuli (in this case, ergonovine). Left ventricular hypertrophy, commonly seen in advanced hypertension, can impair coronary reserve,[16] perhaps via external compression of vessels.

Thus, one might hypothesize that hypertensive patients with a lesser degree of coronary reserve, a narrowed artery, and a diastolic pressure below a critical threshold will risk a jeopardized myocardium and ischemic events. Indeed, hypertensive patients are likely exposed to much lower pressures than are measured in the office. Ambulatory pressures are usually lower than clinic pressures, especially when measured by doctors rather than other health care workers: the "white coat" effect.[17] Night pressures can fall abruptly, putting hypertensive patients at risk during sleep.[18] This is a strong argument for keeping diastolic office pressures above 80 mm Hg.

Figure 2. **Relative risk of mortality from myocardial infarction as a function of treated diastolic pressure among patients with and without prior ischemic heart disease:** *The lower risk group exhibits a continuous relationship; those with prior infarction show the J-curve.*

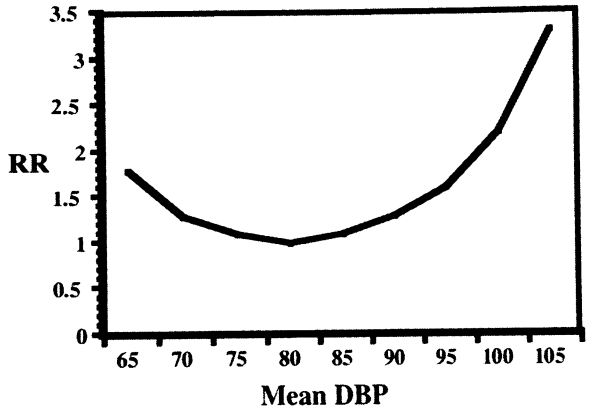


Reprinted with permission from Cruikshank et al.[5]

Drug therapy, while effective in preventing strokes, has failed to show a consistent reduction in coronary events in most of the large interventional trials. This has sometimes been blamed (rightly or wrongly) on using β-blockers and diuretics, which can raise cholesterol levels and oppose coronary

risk reduction from pressure lowering. Alternatively, the J-curve, indicating an increase in coronary events at lower diastolic pressures, might explain this observation. There is no proof yet for either contention. However, the latter hypothesis agrees with the observation that both autoregulatory flow reserve and the ability to increase oxygen extraction are less in the hypertensive patient's heart than brain.[19]

Figure 3. **Relative risk of coronary event at varying diastolic pressure levels in treated Swedish hypertensive patients**



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Reprinted with permission from Samuelsson et al.[6]

Recommendations

Moderate and severe hypertension indicate a need for drug therapy. Guidelines from the World Health Organization[20] and the Canadian Hypertension Society[21] for treating mild hypertension (diastolic < 105 mm Hg) are a reasonable, balanced approach to the initiation of therapy. They differ only in that the WHO recommends drug treatment at 95 mm Hg diastolic whereas the CHS uses 100 mm Hg for those without other risk factors or established target organ complications. Pressures need to be confirmed on multiple visits with a mercury sphygmomanometer and the appropriate size cuff. Nonpharmacologic measures should be addressed. Once the decision has been made to initiate therapy, BP and side effects of therapy should be monitored during follow up.

A target should be set for all patients. In view of evidence suggesting that the J-curve exists, we try for diastolic pressures in the range of 80 to 90 mm Hg. Where the J-curve has been shown to exist, this range shows the most benefit. Aiming for a slightly higher range will avoid overshooting into a lower, potentially dangerous range. Because prior coronary disease might be important, a careful history, physical examination, and electrocardiography should be done to identify higher risk patients for less aggressive therapy. Once in the target range, we reevaluate BP levels regularly to try to keep patients on the least medication to maintain target pressures.

Conclusion

It is difficult to make firm recommendations because of the conflicting results of clinical trials. Even more striking are the opposing interpretations that can arise from looking at the same data in different ways. More studies (eg, the Hypertension Optimal Treatment, or the "HOT" trial) are being carefully designed to help determine the best range for treated blood pressure levels, but these trials will be expensive, and results will take a long time.

For now, it is reasonable to try for diastolic pressures in the 80 to 90 mm Hg range and avoid lower pressures, especially in those with evidence of prior coronary artery disease. One should also be alert for markers of decreased perfusion to other organs, such as the brain (orthostatic hypotension) and kidneys (rise in urea and creatinine levels) ■

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