Is there a J-curve for hypertension and cardiovascular disease? 
How low can one go?

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Abstract

Guidelines on management of hypertension have laid down the blood pressure levels at which one should start treating hypertension and what should be the goals. There is an ongoing debate whether the relationship between BP levels and cardiovascular events is a linear one or J-shaped. There are studies to support either side. While some argue that lower is better, some advocate caution that beyond a particular point of low BP, there is an increased risk of cardiovascular events. J-curve probably exists for diastolic blood pressure in an elderly patient with hypertension and coronary artery disease. However, recent studies published this year seem to counter the concept of J-curve phenomenon.

Key Words
- CVD
- Hypertension
- J-curve

Introduction

The term J-curve is commonly used in the world of economics, where the openness of the economy of the nation shows a J-shaped relationship with the political stability of the country and many believe that the J-curve is a new way to understand why nations rise and fall!

In the field of hypertension, we are going to look at the relationship between the blood pressure (BP) levels and cardiovascular (CV) event rates. The J-curve phenomenon is a paradoxical increase in morbidity and mortality with an excessive decrease in BP.

BP treatment guidelines have recommended BP thresholds to commence treatment and also the BP goals have been defined. However, there is a debate as to how low one can go to achieve optimal benefit from treatment.

There is a concern that the therapeutic harm/benefit equation might tilt towards harm if there is aggressive BP lowering in certain individuals, in certain situations and in certain organs. The debate of J-curve phenomena started in 1979 and there is still no definitive answer.

Factors supporting the J-curve phenomenon

Though there is no undisputable evidence for the existence of the J-curve phenomenon, it is supported by common sense (BP value below which organ perfusion is compromised is bound to exist), physiological data, and observational studies.

J-curve may have different pathophysiological mechanisms such as:
- It may be an epiphenomenon of a more severe underlying disease, low BP being a marker of the illness, thereby increasing mortality
- Low BP may be due to underlying impaired cardiac function

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• J-curve may be seen in patients with increased arterial stiffness, low BP being a marker of high pulse pressure, and hence, the increase in mortality
• J-curve phenomenon may truly be existing

Physiological data
The effects of reducing coronary perfusion pressure by intravenous infusion of nitroprusside on coronary blood flow (measured in the great cardiac vein) were studied in hypertensive patients with and without left ventricular hypertrophy (LVH). In hypertensive patients without LVH, there is no decrease in coronary blood flow till the coronary perfusion pressure of 70 mmHg. Whereas in patients with LVH, the coronary flow showed significant fall with coronary perfusion pressure at 90 mmHg (Figure 1).

This also has a clinical correlation where studies have shown that the CV event rates have a J-shaped relationship with diastolic BP levels in patients with coronary artery disease (CAD) who did not undergo coronary revascularization compared with those who were revascularized (Figure 1).

Clinical studies
In the INVEST study, 22,576 patients of hypertension with CAD were studied and the incidence of myocardial infarction (MI) clearly showed the J-curve phenomenon (almost U-shaped), whereas incidence of stroke did not show the J-curve.

Data from the ONTARGET trial showed that patients who showed BP reduction to less than 130/80, more often exhibited J-shaped response during their visits (Figure 2).

In the INVEST study, the data on 6400 patients of diabetes compared the outcome in subjects in whom systolic BP remained 140 mmHg or more, with those where systolic BP was reduced to between 130 and 139 and less than 130 mmHg. The all-cause mortality increased in patients with systolic BP less than 120 mmHg.

The PROVEIT trial studied 20,332 patients with a history of stroke. The group with on-treatment BP values between 130 and 139 mmHg was taken as reference. The patients with systolic BP more than 150 mmHg showed decreasing risk of CV events up to the reference level of 130 to 139. Systolic BP levels falling below the reference levels again showed an increase in risk of CV events.

In TNT study on 10,001 patients of CAD, low BP (110–120/60–70) portends an increased risk of future CV events (other than stroke) (Figure 2).

Evidence against the J-curve phenomenon:
In a study of 61 prospective trials involving one million adults in the age group of 40 to 89 years with no previous vascular disease, it was clearly shown that systolic blood pressure (SBP) and diastolic blood pressure (DBP) are strongly and directly related to vascular and overall mortality without evidence of threshold down to 115/75 mmHg.

In the UKPDS trial, effect of BP control was studied between patients with tight (BP 144/82 mmHg) vs. less tight (154/87 mmHg) control. These were 1148 Type II diabetic patients with 9 years follow up. Patients with tight control of BP showed significant risk reduction in stroke, heart failure, microvascular disease, any diabetic-related endpoint, and diabetes-related deaths.

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Figure 1: A) The effects of reducing coronary perfusion pressure by intravenous infusion of nitroprusside on coronary blood flow (measured in the great cardiac vein) in hypertensive patients with and without LVH. B) the CV event incidence at different achieved diastolic blood pressure (DBP) levels in patients with coronary artery disease (CAD) who did not undergo coronary revascularization compared with those who had the procedure.

Figure 2: J-curve in the (A) ONTARGET and (B) TNT studies

Figure 3: Unadjusted (A) and adjusted (B) relation between achieved (average in-treatment) DBP and risk of primary outcome in hypertensive patients with coronary artery disease enrolled in the International Verapamil-Trandolapril Study

Limitations of the studies supporting the J-curve
Following are limitations of the studies supporting J-curve
• Lack of randomization: In the INVEST study, compared to patients with DBP 81–90 mmHg, those with less than 60 mmHg were 10 years older, had previous MI, stroke, heart failure, diabetes, and cancer.
• There were a small number of patients with low or very low achieved BP, i.e., a small number of patients in the ascending limb of J-curve. In the INVEST study, a DBP of less than 60 mmHg was seen in 176 patients of 22,576 patients, and in TNT study, a BP of 110/60 or less was seen in 396 patients out of 10,001 patients.
• Most of the studies are observational data and post hoc analysis. Some of the results were unadjusted for confounding variables.
• J-curve may be seen in patients with increased arterial stiffness, low BP being a marker of high pulse pressure, and hence, the increase in mortality.  
• J-curve phenomenon may truly be existing.

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• Most of the studies are observational data and post hoc analysis. Some of the results were unadjusted for confounding variables.
Organ heterogeneity
ONTARGET study included 25,620 high or very high CV risk hypertensive patients. The unadjusted risk of CV events and MI showed a J-curve phenomenon but not the risk of stroke.12

Again there is no evidence of the J-curve phenomenon for renal events when the BP was lowered in type II diabetic patients after adjusting for age, gender, duration of diabetes, glycosylated hemoglobin, currently treated hypertension, ECG abnormalities, dyslipidemia, BMI, smoking, alcohol use, and study drug.

Cerebral autoregulation is probably more effective than the coronary autoregulation. Moreover, coronary circulation occurs mostly during diastole.

New studies
There are three new studies available and it is to be seen whether these contribute to clarity or confusion to the present debate.

• SPRINT: In this study, 9,300 patients were randomized into two treatment strategies of intensive BP control (SBP of 120 mmHg or less) vs. standard BP control (SBP target of less than 140 mmHg).13 Patients with diabetes, those with a history of stroke, and subjects less than 50 years of age were excluded. The study was prematurely stopped because there was a statistically significant 30% reduction in the primary composite endpoint and 25% reduction in all-cause mortality with intensive BP control. The benefit in primary endpoint was mostly driven by decrease in the risk of heart failure and mortality. There was no significant benefit in the risk of stroke, MI, or acute coronary syndrome (ACS). However, this came at the cost of increased incidents of syncpe, electrolyte abnormalities, and acute kidney injury.

• New ACCORD Data (ACCORDIAN): The main ACCORD trial after 4.9 years of follow up had shown a nonsignificant 12% reduction in composite CV events and a significant effect on stroke with intensive BP control.14 Further, 3,957 patients were followed for an additional 54 to 60 months. There was a 9% nonsignificant reduction in primary CV events. There was a benefit of intensive BP lowering in patients randomized to standardized glycemic therapy. These results fit well with SPRINT study, and support SBP lowering to 120 mmHg in patients with high CV risk or diabetes.

• A meta-analysis of 19 trials involving 45,000 patients showed that intensive BP lowering (BP achieved 133/76 mmHg) significantly reduced major CV events, stroke, MI, albuminuria, and retinopathy progression.15 But there was no benefit in heart failure, CV death, total mortality, or end-stage renal disease compared with less intensive BP lowering strategy (BP achieved 140/81). The BP levels are different and the benefits are different compared to SPRINT.

What should we do?
In patients with elevated DBP and CAD with evidence of myocardial ischemia, the BP should be lowered slowly, and caution is advised in inducing decreases in DBP to <60 mmHg in any patient with diabetes or who is more than 60 years of age.

In older hypertensive individuals with wide pulse pressures, lowering SBP may cause low DBP values (less than 60 mmHg). This should alert the clinicians to assess carefully any untoward signs or symptoms, especially those resulting from myocardial ischemia (Class IIa, C).

The BP targets recommended for patients with CAD are as follows:

- General CAD prevention: <140/90 mmHg
- High CAD risk: <130/80 mmHg
- Stable angina: <130/80 mmHg
- LV dysfunction: <120/80 mmHg
- ACS: <130/80 mmHg
- LS: <120/80 mmHg

In patients with stroke/TIA, it is reasonable to achieve a SBP of less than 140 and DBP of less than 90 (Class IIa, B).

In patients with a recent lacunar stroke, it is reasonable to target a SBP of less than 130 mmHg.16

Summary
If one ventures to summarize the available data, the following points emerge:

• J-curve phenomenon may be an epiphenomenon (“reverse causality” as in comorbid conditions, poor LV function, or arterial stiffness states) or in certain situations, a reality.

• Coronary circulation is unique with its dependency on diastole. Here, probably a J-curve phenomenon is likely to play a role, particularly in hypertensive patients who are old and not completely revascularized. Caution is to be exercised not to lower DBP below 60 mmHg.

• The concern about J-curve phenomenon should not discourage clinicians from following guidelines in controlling hypertension and reach reaching targets recommended because, currently, BP control in the hypertensive population is disarmingly low.

References

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