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COMMENTARY

Hypertension and the J-curve phenomenon: implications for tight blood pressure control

Fabio Angeli, Gianpaolo Reboldi and Paolo Verdecchia

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The term J-curve is used in several fields of science to refer to a variety of J-shaped diagrams where a curve initially falls, but then rises to higher levels. In cardiovascular (CV) medicine, the J-curve phenomenon arises when a risk factor becomes inversely related to risk below a certain point, whereas the more widely accepted positive risk association exists across most of the observed risk factor distribution. In simpler terms, when elevated blood pressure (BP) is lowered, the risk of CV events decreases, but lowering BP below a critical 'nadir' is no longer beneficial and possibly deleterious, thus shaping a J-curve.

This phenomenon was originally described for diastolic BP by Stewart[1] in 169 well-matched hypertensive patients treated and followed for 6.25 years. At the end of the study, the incidence of myocardial infarction (MI) was five times higher in the patients with achieved diastolic BP < 90 mm Hg, compared with those who reached a diastolic BP of 100–109 mm Hg ($P < 0.01$).

Similar observations have been reported later by Cruickshank *et al.*[2] on 902 hypertensive patients treated with atenolol in combination with other drugs and followed for a mean of 6.1 years. They observed a J-curve relationship between diastolic BP, and MI and death in patients with coronary artery disease (CAD).

More recently, some *post-hoc* analyses of randomized clinical trials documented a J-shaped relationship between systolic BP and the risk of CV events (Figure 1, left panel) and cast doubts to what level the systolic BP should be lowered to optimize treatment.[3]

On the contrary, there are some studies where such an effect has not been clearly demonstrated[3–5] (Figure 1, right panel). For example, in the physicians and women's studies by Glynn *et al.*,[4] no J-curve effect for CV disease was noted in both women and men.

In the Cardiovascular Health Study,[5] after adjustment for potential confounders, systolic and diastolic BP were directly associated with the risk of incident MI and stroke. In the adjusted model for MI, a 1-standard deviation (s.d.) change in systolic and diastolic BP was associated with hazard ratios (HRs) of 1.24 (95% confidence interval (CI): 1.15–1.35) and 1.13 (95% CI: 1.04–1.22), respectively. For stroke, the HRs were 1.34 (95% CI: 1.21–1.47) with systolic BP and 1.29 (95% CI: 1.17–1.42) with diastolic BP. The associations between systolic and diastolic BP levels and CV disease risk were generally linear; specifically, there was no evidence of a J-shaped relationship.

The same study also showed any increase in CV complications with decrease in pulse pressure (PP).

Specifically, in multivariable models a 1-SD change in PP was associated with HR of 1.21 (95% CI: 1.12–1.31) for both MI or stroke.

MECHANISMS OF J-CURVE

The question is at what pathophysiologic BP range the J-curve may occur. Although the underlying mechanisms which may explain a J-curve association between CV risk and systolic BP are still elusive, some possible explanations have been proposed to link low diastolic BP levels and coronary complications.

As coronary artery perfusion occurs predominantly during diastole, an association could be expected between diastolic BP and coronary artery perfusion. In patients with hypertension and especially in those with left ventricular hypertrophy (LVH), there is an upward shift of the coronary perfusion pressure to 70 mm Hg for hypertensive patients and 80–90 mm Hg for those with hypertension and LVH, compared with normotensive controls of 60 mm Hg. Below these pressures the coronary blood flow decreases and the oxygen extraction increases. In addition, low perfusion pressure is associated to severely impaired coronary autoregulation especially in presence of coronary epicardial stenosis and predisposes to severe ischemia of the subendocardial myocardium or MI[1,2] (Figure 2).

In contrast to the coronary circulation, the cerebral circulation depends mostly on systolic BP. In particular, cerebral blood flow is not seriously affected by low diastolic BP and could explain the lack of a J-curve effect regarding strokes at low diastolic BP in contrast with CV and coronary complications.[5]

NEW INSIGHTS

For more 30 years there has been controversy regarding the clinical significance of the J-curve, especially in individuals receiving antihypertensive therapy and with a history of known CAD. Recently, some effect modifiers in influencing the presence or absence of a J-curve in predicting CV disease risk have been investigated. The results of the study by Yamazaki *et al.*[6] published in the current issue of the Journal add new data in this intriguing area.

F Angeli is at Section of Cardiology, Hospital Media Valle del Tevere, Perugia, Italy; G Reboldi is at Department of Internal Medicine, University of Perugia, Perugia, Italy; P Verdecchia is at Department of Internal Medicine, Hospital of Assisi, Assisi, Italy.
E-mail: fangeli@cardionet.it

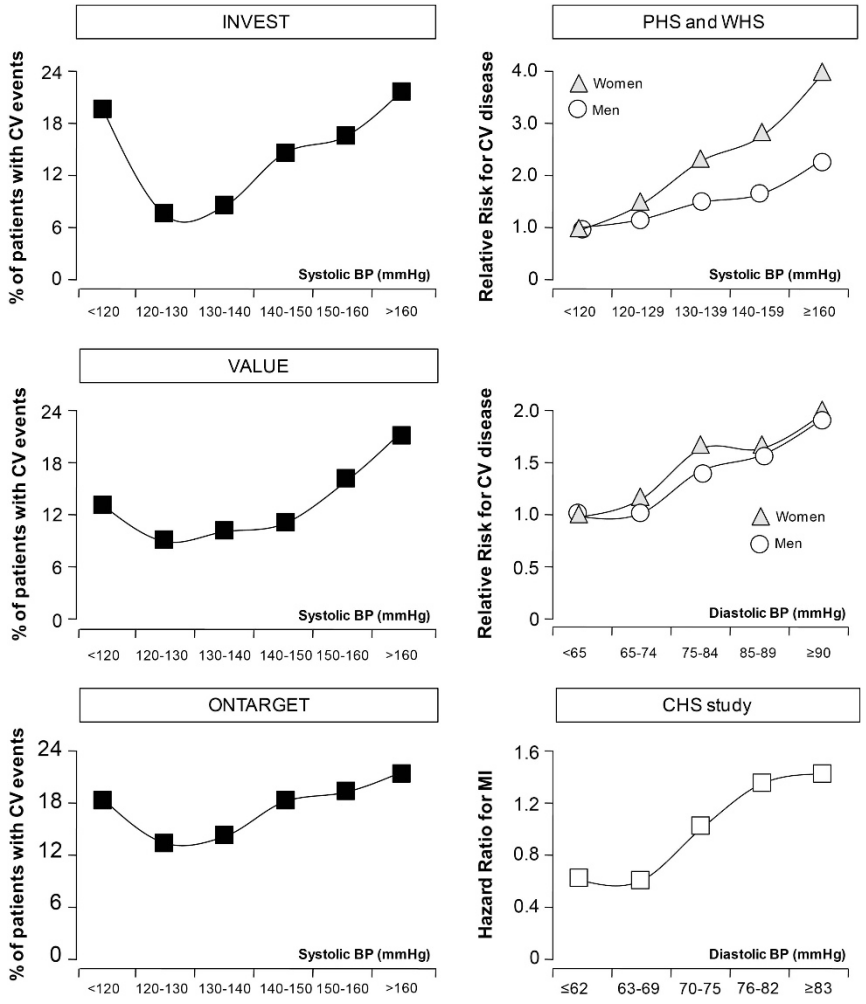

Figure 1 Clinical trials demonstrating a J-curve effect for cardiovascular events (left panel) and clinical studies without clear evidence of the J-curve phenomenon (right panel). Data from references 3–5. Data from The International Verapamil-Trandopril Study (INVEST), Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial, Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), Physicians' Health Study (PHS) and Women's Health Study (WHS) and Cardiovascular Heart Study (CHS).

Briefly, this prospective survey with central registry was designed to investigate drug use among 28 536 hypertensive subjects treated with valsartan. The primary end point was defined as cerebrovascular or cardiac events. The relationship between end points and BP measured at the last visit or before the occurrence of events was performed *post hoc*.

During a median follow-up of 2.93 years, 550 patients developed a cerebrovascular event and 576 a cardiac event. Higher BP achieved during treatment (systolic BP $\geqslant$ 140 mm Hg and diastolic BP $\geqslant$ 90 mm Hg) were stronger risk factors for the incidence of both cerebrovascular and cardiac events and the risks of developing these events were increased in an age-dependent manner.

A weak, but significant, systolic J-curve phenomenon was only observed in elderly patients ($\geqslant$75 years) for cardiac events: subjects with achieved systolic BP $<$ 120 mm Hg showed an HR for cardiac events of 1.90 (95% CI: 1.18–2.99, $P = 0.008$) when compared with hypertensive patients with achieved systolic BP ranging from 130 to 140 mm Hg.

Although intriguing, these findings are open to some observations and should be cautiously interpreted.

First, the results show that aging has an important role as potential effect modifier in influencing the manifestation of a J-curve paradox in hypertension. Notably, elderly patients are more likely to have isolated systolic hypertension (ISH; that is, increased PP), especially in association with CAD and hemodynamically significant coronary artery stenosis. Importantly, PP has been shown to be a marker of increased large artery stiffness and an independent predictor of increased CV disease risk. In the context of this study, low values of systolic BP did not exclude high levels of PP for the coexistence of very low diastolic BP.

Second, antihypertensive therapy in the elderly person with ISH preferentially decreases systolic over diastolic BP, lowers PP, decreases arterial stiffness, and therefore, may improve the coronary oxygen supply/demand ratio of the left ventricle (thereby protecting it from ischemia).

In addition, orthostatic hypotension is relatively common in elderly patients and may be intensified by antihypertensive drugs. Notably, the presence of orthostatic hypotension has been associated with a 3.5-fold increase in the risk of CAD.[7]

Taken together, these observations suggest that the systolic BP J-curve documented in this study is more compatible with reverse causality than with antihypertensive drug overtreatment. Reverse causality occurs when a disease event causes reduction in the primary risk factor (in our case BP), making the event rate appear higher than it should be at lower risk levels. In other words, low systolic BP might be only an epiphenomenon related to an underlying chronic debilitating illness and/or cardiac dysfunction.

Finally, a J-curve for diastolic BP in elderly hypertensives was not observed by the Authors[6] of the study and, consequently, the effect of low diastolic BP on the exacerbation of treatment-induced coronary ischemia is not supported.

COMPARISON OF DIFFERENT BP TARGETS

Only few trials have directly compared BP goals to test the hypothesis that attained BPs below the usual goal of less than 140/90 mm Hg improve outcomes.

In a recent Japanese (JATOS) Study,[8] 4418 older hypertensive patients were randomized to either a systolic BP reduction to $<$140 mm Hg or to $\geqslant$140 mm Hg and followed for 2 years. At the end of the study, there was no difference in the primary end point of CV disease or renal failure between the two groups. Similar observations were also reported from the Action to Control Cardiovascular Risk in Diabetes study,[9] in which there was no difference between the intensively (systolic BP $<$ 120 mm Hg) and less intensively (systolic BP $<$ 140 mm Hg) treated groups with respect to a composite of CV events. However, the incidence of stroke, a

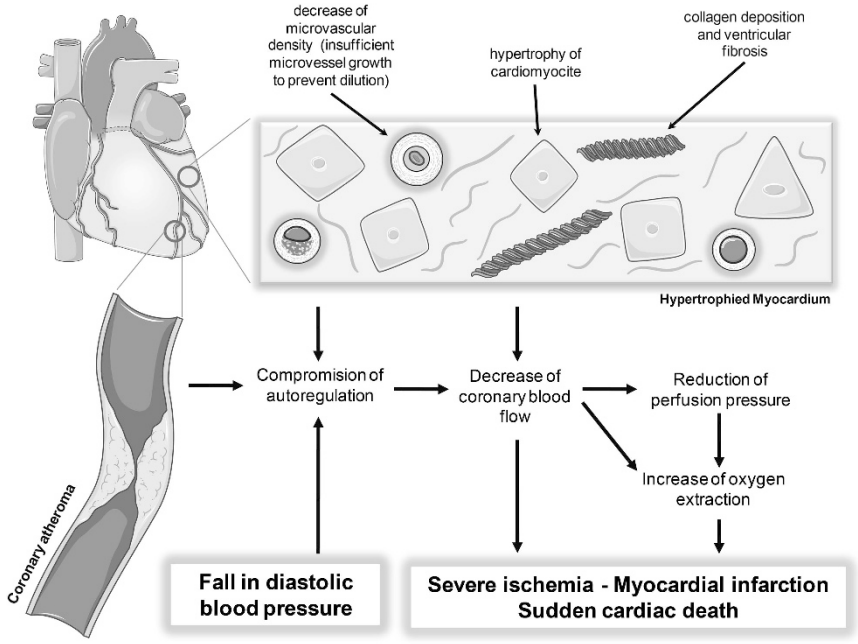

Figure 2 Possible mechanisms that increase the risk of manifesting a J-curve effect with low diastolic blood pressure in patients with coronary artery disease, hypertension and left ventricular hypertrophy. In patients with coronary stenosis, the autoregulation of coronary blood flow is compromised and a fall in diastolic blood pressure might lower the perfusion pressure distal to the epicardial artery stenosis below a critical level at which the autoregulation is no longer functional and the fractional flow reserve is compromised and may lead to myocardial ischemia and myocardial infarction. This is further aggravated with the coexistence of hypertension and left ventricular hypertrophy.

pre-specified secondary end point, was significantly lower in the tight control group.

Conversely, the Studio Italiano Sugli Effetti Cardiovascolari del Controllo della Pressione Arteriosa Sistolica (Cardio-Sis)[10] clearly demonstrated that a tight BP control in non-diabetic patients with hypertension is associated to an improved CV prognosis. In particular, the composite pool of pre-specified CV events and death occurred less frequently in the tight (<130 mm Hg) than in the usual (<140 mm Hg) control group (HR: 0.50;CI: 0.31–0.79; $P=0.003$).[10]

RECOMMENDATIONS IN CLINICAL PRACTICE

Antihypertensive treatment reduces the risk of all CV events across all age and BP strata to a similar extent, and the absolute benefit of treatment increased with age. The standard goal of antihypertensive therapy (that is, $<140/90$ mm Hg) is well established and should be maintained in all hypertensive patients.

Despite their obvious limitations, *post-hoc* analyses of trial data indicate a progressive reduction in the incidence of CV events with progressive lowering of systolic BP down to about 120 mm Hg, and diastolic BP down to about 75 mm Hg, although the additional benefit at low BP values becomes rather small.

A J-curve phenomenon is unlikely to occur until lower values are reached, except perhaps in patients with advanced CAD. In these patients, the optimal BP target remains undefined.

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