Review Article

J-Curve Phenomenon: A Matter of Debate

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Key words: **J-curve, cardiovascular disease, hypertension.**

Manuscript received: January 27, 2012;
Accepted: July 4, 2012.

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There is mounting evidence to confirm that hypertension activates multiple pathophysiological processes that lead to deterioration of the cardiovascular system. Since the reduction of blood pressure (BP) is accompanied by beneficial effects on cardiovascular and renal outcome, especially in subjects with uncomplicated hypertension,[1,2] it has been suggested that lower achieved BP values—close to fully normotensive levels—could decrease the risk of adverse outcomes also in high-risk hypertensive subjects. However, a "J-curve phenomenon" has been observed in such patients, referring to an increased rate of cardiovascular events when BP levels fall below a level that is critical for organ perfusion. Although guidelines for the management of hypertension recommend a BP goal of <140/90 mmHg in the general population and <130/80 mmHg in diabetics, patients with renal, cerebrovascular or coronary artery disease (CAD), or organ damage,[3] the majority of high-risk patients remain with poorly controlled BP.[4] In this review we present data for and against the existence of the J-curve, considering cardiac, cerebral and renal events. We investigate the J-curve among diabetics, patients with renal dysfunction, and elderly subjects. New data challenging the speculation that we should pursue lower achieved BP levels for patients with a high stroke risk than for patients with a high cardiac risk are also analysed.

Historical background

The J-curve issue was first addressed in 1979 in subjects with uncomplicated hypertension. Subjects with achieved diastolic BP (DBP) <90 mmHg had 5 times greater risk of myocardial infarction than those with DBP 100-110 mmHg.[5] In 1987, an analysis of 902 patients with moderate to severe hypertension revealed a J-shaped relationship between the frequency of fatal myocardial infarction and in-treatment DBP, with the lowest frequency at DBP levels 85-90 mmHg.[6] The J-curve was confined to those with evidence of ischaemic heart disease. Another retrospective analysis in 1987 claimed that, for cardiovascular outcomes, there was no additional benefit from lowering BP to <150/85 mmHg in middle-aged hypertensive men.[7]

J-curve and cardiac events

Evidence derived from studies in subjects without vascular disease supports the existence of a linear relationship between BP levels and cardiovascular morbidity and mortality. Data from a large cohort of the MRFIT study—including mildly hypertensive patients with low cardiovascular risk—showed a direct relationship between DBP and risk of CAD or stroke without evidence of any threshold below which the association was inverted (within the range of 70-110 mmHg).[1] In a large

meta-analysis involving one million adults with no previous vascular disease recorded, BP up to at least 115/75 mmHg proved to be strongly and directly related to vascular and all-cause mortality.[2] On the other hand, tighter BP control seems also to be cardioprotective in high-risk patients. In a recent study,[8] treated non-diabetic subjects with systolic BP (SBP) ≥150 mmHg were randomly assigned to a goal of SBP<140 (according to hypertension guidelines) or <130 mmHg (tight control). In both patients with and without prior cardiovascular disease the secondary endpoint of fatal and non-fatal cardiovascular events was less frequent in the tight than in the standard BP control group. Among 234 hypertensive subjects with a diagnosis of angina pectoris and angiographically confirmed coronary artery lesions there was no J-curve for DBP in the range of 74-105 mmHg,[9] but the lower the DBP, the better the prognosis.

However, studies in patients with a history of vascular disease raise the issue of the existence of a "J-curve phenomenon", since treatment-induced aggressive BP lowering may be deleterious for the heart. Therefore, 13 studies of treated hypertensive subjects demonstrated a J-shaped relationship for cardiac events and DBP, which was steeper in those with pre-existing ischaemic heart disease.[10] One of the problems with these studies was their retrospective character, and also the fact that none of the available outcome-based studies was primarily designed to compare different BP goals in patients with CAD. In the HOT study, which included treated hypertensive patients, the subjects were randomly assigned to target DBP<90, <85 or <80 mmHg. The lowest incidence of cardiovascular events was at mean BP levels 139/82.6 mmHg and the lowest risk of cardiovascular death was at mean DBP 86.5 mmHg. Additional BP reduction below DBP 82.6 mmHg was not beneficial, but it was safe.[11] However, a *post hoc* analysis of the HOT study showed that, in the subgroup with ischaemic heart disease, there was a J-curve relationship between DBP and risk of myocardial infarction, since the frequency of myocardial infarction increased when DBP was lowered below 83 mmHg.[12]

The role of antihypertensive treatment in the causality of the J-curve phenomenon has also been vigorously debated. The question is whether over-treatment causing low BP leads to organ-hypoperfusion, or whether there are comorbidities responsible for low BP levels and for adverse outcomes (reverse causality). The VALUE study, of patients who were hypertensive and at high cardiovascular risk, showed that the treatment-induced reduction of SBP to <120 mmHg was associated with an increased, rather than a decreased risk of cardiovascular events.[13,14] Results from the Framingham study cohort support the existence of a J-curve relationship for DBP and CAD deaths in patients with myocardial infarction, for both treated and untreated subjects.[15] In low-risk patients the relationship was linear. A meta-analysis of seven randomised clinical trials from the INDANA database showed than in hypertensive patients the J-shaped relationship between SBP/DBP and cardiovascular mortality was independent of the antihypertensive treatment.[16] The J-curve occurred with a nadir of DBP 80 mmHg in treated patients and a nadir of DBP 85 mmHg in those receiving placebo. The TNT trial, which enrolled patients with CAD and low LDL-cholesterol levels, exhibited a J-curve relation between SBP and DBP and fatal or non-fatal cardiovascular events, with a nadir of 146.3/81.4 mmHg; there was an exponential increase in the risk of the primary outcomes for BP<110-120/60-70 mmHg, except for the outcome of stroke.[17] It is important that these results are from a trial of lipid-lowering rather than antihypertensive treatment. Patients with BP in the lowest part of the range were prone to a higher incidence of cardiovascular events, despite there being no substantial change in their antihypertensive therapy.[18]

The INVEST study demonstrated a J-curve relation between SBP and DBP and the primary outcomes (death, myocardial infarction, stroke) in hypertensive patients with stable CAD.[19] The diastolic J-curve was more pronounced than the systolic, with an increased risk of myocardial infarction and death (and, to a much lesser extent, of stroke) for DBP<75 mmHg. While a progressive reduction of achieved SBP to 120 mmHg was related to a reduction in stroke, for SBP levels <130 mmHg the risk of myocardial infarction showed a J-curve phenomenon. However, subjects in the lowest achieved DBP range were older, had higher pulse pressure, and a greater incidence of prior heart disease and diabetes. Consequently, the issue is whether the increased frequency of adverse cardiovascular outcomes is attributable to the already overburdened general health condition of these subjects or to the excessive reduction in BP.[20,21] Along the same lines, in a recent study of patients with clinically manifest vascular disease (SMART), BP levels above and below 143/82 mmHg proved to be an independent risk factor for recurrent vascular events.[22] Notably, high SBP was associated with a

more favourable prognosis in patients with a recent diagnosis of CAD, age >65 years, and patients whose pulse pressure was >60 mmHg. Therefore, although the relationship between vascular events and mean SBP, DBP, and pulse pressure was J-shaped, its causative character warrants further investigation. In the ONTARGET study, although it was not designed to test the effect of different BP goals on cardiovascular outcomes, a J-curve, with a nadir of 130 mmHg, occurred in the relationship between in-treatment SBP and myocardial infarction, cardiovascular mortality, but not stroke, in well-treated, high-risk patients with atherosclerotic disease or diabetes with organ damage.[23] Patients with lower values of BP at entry were also characterised by an increased incidence of risk factors. It is notable that in subjects with baseline SBP≥140 mmHg the reduction of BP did not inversely affect the cardiovascular outcome, but in patients with baseline SBP<130 mmHg, adjusted for several covariates, cardiovascular mortality increased with a further SBP reduction ($p<0.0001$). Therefore, it is debatable whether the "low achieved" BP levels or the treatment-induced "reduction" in BP levels are related with a higher risk of cardiovascular outcomes in hypertensives with ischaemic heart disease.

J-curve and stroke

The risk of a primary stroke is linearly and strongly related to both SBP[24] and DBP[1] levels. An analysis of 9 prospective studies showed that within the range of DBP 70-110 mmHg there was no evidence for a threshold level below which the risk of stroke or CAD increased.[1] BP lowering is an established therapy for the primary prevention of stroke.[25] Moreover, studies of patients at high risk of stroke without established symptomatic cerebrovascular disease, like ONTARGET,[23] IDNT,[26] or the TNT trial,[17] found a J-curve phenomenon relating BP levels and cardiovascular events, but for the outcome of stroke "lower was better", even for levels of SBP as low as 110 mmHg.[23] In a recent meta-analysis of 73,913 patients with diabetes, more-tight BP control compared with less-tight BP control reduced the risk of stroke by 31%.[27] The risk of stroke decreased by 13% for each 5 mmHg reduction in SBP, and by 11.5% for each 2 mmHg reduction in DBP ($p<0.01$). The ACCORD study recently detected a significantly lower annual rate of stroke in the intensive therapy group targeting SBP<120 mmHg, compared with the group targeting SBP<140 mmHg.[28] The population consisted of diabetic patients at high cardiovascular risk and there was no cardiovascular protective benefit for SBP<120 mmHg. It is possible that cerebral autoregulation can be more effective than that of the heart, meaning a better ability of the brain to preserve blood flow and tissue perfusion when BP is substantially reduced by treatment.

On the other hand, there are limited data on the impact of BP lowering on secondary prevention of stroke. A retrospective analysis of the UK-TIA trial, including patients with history of ischaemic stroke or transient ischaemic attack, showed a direct and continuous relation between stroke and both SBP and DBP, with no evidence for the existence of a J-curve.[29] The same notion was supported in the PROGRESS study among patients with cerebrovascular disease, showing that the lowest risk of recurrence was among the one quarter of subjects with the lowest follow-up BP levels (median 112/72 mmHg).[30] The continuous association of achieved follow-up SBP levels with stroke incidence was independent of treatment and baseline BP.

Although most studies support the absence of a J-curve association between BP lowering and cerebrovascular events, the IST study found that in patients with confirmed ischaemic stroke low-normal SBP<120 mmHg was associated with an increased risk of early recurrence by 2 weeks and an excess of early deaths from CAD compared to high-normal SBP.[31] Therefore, there is a hint, although statistically non-significant, of a J-curve relationship between SBP and stroke recurrence. A recent study in patients with acute stroke and raised blood pressure (SBP≥140 mmHg) suggested a higher risk of poor functional outcome after 6 months in the group undergoing careful BP-lowering treatment with candesartan, compared to the placebo group.[32] In a trial involving 20,332 subjects with recent ischaemic stroke, telmisartan-induced BP lowering did not significantly lower the rate of recurrent stroke, major cardiovascular events or diabetes.[33] In this setting, a recent *post hoc* observational analysis of a multi-centre trial involving patients with recent non-cardioembolic ischaemic stroke (PROFESS) categorised the patients according to mean SBP level: very low-normal (<120), low-normal (120-129), high-normal (130-139), high (140-149) and very high (≥150 mmHg).[34] The risk of first recurrence of stroke and of further cardiovascular events was significantly higher for patients with mean SBP very low-normal (<120) than for patients with SBP high-normal (130-139 mmHg). The frequency of hypertension (53.7% to 85.6%), diabetes

(22.4% to 35.1%), and use of antihypertensive drugs at baseline increased steadily across the 5 groups. The J-curve relation of SBP to vascular risk after stroke could be attributed to reverse causality. However, the results were adjusted for major health conditions (e.g. stroke subtype, heart failure) as well as for baseline BP, and the findings were also independent of follow-up BP and multiple antihypertensive medications. Although the aforementioned data suggest the existence of thresholds of benefit or harm in SBP levels after stroke, more clinical trials are required. The ongoing PODCAST trial[35] and the Secondary Prevention of Small Subcortical Strokes trial (SPS3),[36] examining the impact of low versus higher achieved SBP levels in stroke patients, may provide us with more data to elucidate the issue of J-curve and stroke risk.

Does a J-curve exist for renal outcome?

It is widely accepted that systolic hypertension is associated with the progression of kidney disease. The target for BP-lowering therapy is to slow the rate of chronic kidney disease (CKD) progression and the risk of cardiovascular disease, which together constitute the cardiorenal risk.[37] However, randomised, prospective studies investigating the impact of more aggressive BP goals (<130/80 mmHg) on slowing CKD progression are scarce. A meta-analysis of 9 prospective, randomised trials involving adults with hypertension showed a direct and continuous relationship between BP levels and kidney disease progression, with the smallest decline in glomerular filtration rate (GFR) occurring with an achieved mean BP of 125/75 mm Hg.[38] A recent cohort study that enrolled 218 older, hypertensive veterans with CKD who were followed up for 7 years, revealed a J-shaped relationship between BP levels and all-cause mortality, but not for end-stage renal disease.[39] Mortality increased when BP was reduced to below 110/70 mmHg, while the relationship between baseline SBP and DBP and end-stage renal disease was monotonic (the lower the better). Notably, the J-curve for mortality was more evident in patients with age >65 years, advanced CKD, and an absence of clinical proteinuria. In agreement with the previous results was the ADVANCE trial, which included >11,000 diabetic subjects and showed that renal events were progressively less common as SBP fell to the level of 110 mmHg,[40] with the lowest risk for renal events observed among participants with achieved SBP <110 or DBP 65 mmHg. The benefit remained for the patients with initial SBP levels <140, or even <120 mmHg.[41]

Renal perfusion occurs mainly in systole, thus the J-curve phenomenon, at least for DBP, does not seem to be applicable for renal outcomes. However, the MDRD trial proved no benefit of the lower BP goal in slowing CKD progression in subjects with non-diabetic nephropathy (GFR<39 ml/min).[42] After 1 year of follow up among patients with proteinuria >1 g/day, the subjects with low BP levels (mean SBP during follow up 126 mmHg) exhibited a significant reduction in CKD progression.[43] Similar results were derived from the AASK trial in African-American subjects with GFR 20 to 65 ml/min/1.73 m^2 and albuminuria.[44] Lower BP levels (128/77 mmHg) were not related to a slowing of CKD progression, but there was a slower decline in GFR among the subset of patients with proteinuria >1 g/day.[45] Therefore, lowering BP levels to <130/80 mmHg is associated with a beneficial renal outcome mainly in patients with advanced proteinuric nephropathy, but not for subjects with CKD as a whole.[37]

On the other hand, a meta-analysis of 11 randomised trials including 1860 patients with mainly non-diabetic kidney disease showed that the lowest risk for renal disease progression was associated with SBP levels 110-129 mmHg. SBP<110 mmHg may be associated with a higher risk for kidney disease progression.[46] These data imply that the J-curve phenomenon has not been proven with respect to renal outcomes, but studies raise the issue of possible adverse effects of aggressive BP lowering on renal outcome.

J-curve in certain populations

Diabetic subjects

Data in diabetic, hypertensive subjects have demonstrated a benefit from lower achieved BP levels; the UKPDS results, for example, showed that patients with tight BP control (achieving mean BP 144/82 mmHg) had reduced macrovascular and microvascular events.[47] An already mentioned meta-analysis in diabetics also confirmed the reduction of stroke risk with tighter compared to less tight BP control.[27] On the other hand, although guidelines for the management of hypertension recommend the goal of <130/80 mmHg for diabetics, a reappraisal of European guidelines in 2009 underlined that studies supporting the beneficial effect of SBP<130 mmHg are

almost nonexistent.[48] Indeed, in the studies among diabetic hypertensive patients, achieved in-treatment SBP remained >130 mmHg, apart from the ABCD trial,[49] which demonstrated no difference in cardiovascular risk between the group with a mean SBP of 138 versus the intensive group of 132 mmHg. The ACCORD study,[28] which proved there was no significant reduction in cardiovascular outcomes from reducing SBP to 119 versus 133 mmHg, and the ADVANCE study, which showed that for the composite endpoint of micro- and macrovascular events the benefit accompanied the reduction of SBP within the range of 130-140 mmHg,[50] indicate that, at least in diabetics, the benefit of BP lowering gradually flattens at lower BP levels.[18] Meta-analyses of 13 randomised clinical trials in 37,736 type 2 diabetic subjects or subjects with impaired fasting glucose proved that the intensive BP control group (≤135 mmHg) exhibited a similar reduction of macro- and microvascular events (cardiac, renal, and retinal) to that of the standard BP control group (≤140 mmHg).[51] With a more aggressive BP goal (≤130 mmHg) the stroke risk continued to fall, but there was no benefit regarding the risk of other vascular events. The J-shaped relationship between BP levels and cardiac events was demonstrated in a meta-analysis of 13 studies, which included diabetic and non-diabetic subjects but performed an adjustment for diabetic status.[10] In a subgroup analysis of the INVEST study, limited to diabetic subjects with CAD, in-treatment SBP 130-140 mmHg was associated with a reduced risk of cardiovascular events compared with SBP>140 mmHg.[52] Lower SBP levels (<130 mmHg) were not associated with any further reduction in cardiovascular mortality; on the contrary, the all-cause mortality increased when compared to the "usual treatment" group (SBP 130-139 mmHg) and there was a J-curve with a particularly evident rise in cardiovascular events towards levels of achieved SBP<120 mmHg. The Botnia study of elderly, diabetic subjects observed a U-shaped association between pulse pressure and mortality, especially in patients with a positive history of cardiovascular disease.[53] The recent ROADMAP study showed that, among patients with pre-existing CAD, those in the lowest and the highest quartiles of SBP reduction during the double-blind treatment period had the highest rates of cardiovascular death.[54] SBP<120 mmHg possibly showed a J-shaped increase in cardiovascular mortality in the olmesartan group, while there were no interactions with DBP.

Subjects with CKD

Guidelines for the management of essential hypertension recommend a BP goal <130/80 mmHg for patients with CKD.[3] The IDNT trial provided evidence that, among hypertensive subjects with overt diabetic nephropathy, achieved SBP levels below 120 mmHg were associated with an increased cardiovascular mortality rate and heart failure hospitalisation rate.[26] Moreover, below the threshold of achieved DBP 85 mmHg there was a trend for all-cause mortality to increase and for every 10 mmHg further reduction in DBP the risk of myocardial infarction increased, while there was no J-curve phenomenon for stroke risk. A study in patients with GFR<60 ml/min/1.73 m^2 showed that SBP levels <133 mmHg and DBP levels <65 mmHg were associated with a higher mortality compared to higher BP levels.[55] The already mentioned study in veterans with CKD confirmed a J-shaped relationship with total mortality, especially for subjects with advanced CKD, but not with end-stage renal disease.[39] Regarding the stroke risk, a sub-analysis of the PROGRESS study, involving 1757 subjects with stage 3 or greater CKD, showed that treatment-induced BP lowering prevented recurrent stroke with no evidence of a J-curve.[56]

Elderly with isolated systolic hypertension

Even though trials in the elderly have shown a reduction in cardiovascular events in actively treated patients, the in-treatment SBP in most of the trials remains >140 mmHg.[41] Despite the results of studies showing that in relatively healthy elderly patients BP goals of <140 mmHg are safely achievable,[57] there are studies advocating the occurrence of a J-curve. The Syst-Eur trial in elderly patients with isolated systolic hypertension demonstrated a J-shaped relationship between DBP and cardiovascular events only for patients with baseline CAD, which was not confounded by the achieved SBP.[58] The results of the SHEP trial showed that, for the active treatment group only, a decrease of 5 mmHg in DBP increased the risk of stroke, CAD, and cardiovascular disease.[59] A lower DBP was associated with an increased incidence of cardiovascular disease, with significant effects observed first at 70 mmHg and then more strongly at 60 mmHg or below. Indeed, for DBP<55 mmHg the relative risk approaches a 2-fold increase. The ZODIAC study did not show a J-curve, but for every 10 mmHg decrease in SBP and DBP the mortality risk increased by 20% and 26%, respectively, in elderly, diabetic patients.[60]

Table 1. Studies favouring a J-shaped relationship between BP levels and outcomes

Study (year)	n	Included subjects	J point (nadir), mmHg	Events related in J-shaped manner with BP	Comments
SMART[22] (2012)	5788	Symptomatic vascular disease (CAD, CVD, PAD)	SBP/DBP: 143/82, PP: 62	Vascular events (MI, stroke, vascular death) and all-cause mortality.	Elevated BP not associated with higher vascular event rate and mortality in patients with recent diagnosis of CAD, >65 yrs, PP >60 mmHg.
PROFESS[34] (2011)	20,330	≥50 yrs, recent non-cardioembolic ischaemic stroke	SBP: 120	First recurrence of stroke (any type).	Results adjusted for major health conditions (stroke subtype, heart failure), baseline BP and independent of follow-up BP, antihypertensive medication.
ROADMAP[54] (2011)	4447	18-75 yrs, type 2 DM	SBP: 120	Cardiovascular mortality.	Only among patients with pre-existing CAD, those in the lowest quartile of SBP and those in the highest quartile of SBP reduction during the double-blind treatment period had the highest rates of cardiovascular death.
PROVE IT-TIMI 22 trial[66] (2010)	4162	Acute coronary syndrome patients	SBP/DBP: 136/85 (range 130-140 for SBP and 80-90 for DBP)	Composite of all-cause death, MI, unstable angina, revascularisation after 30 days, stroke.	The curve was relatively flat for SBP 110-130 and DBP 70-80; therefore, too low BP goals (especially <110/70 mm Hg) may be dangerous.
INVEST Subanalysis[52] (2010)	6400	hypertension, CAD, type 2 DM	SBP: 130	All-cause mortality.	Rise in mortality, particularly evident towards levels of achieved SBP<115 mmHg.
TNT[17] (2010)	10,001	35-75 yrs, clinically evident CAD and LDL<130 mg/dl	SBP/DBP: 146.3/81.4	Cardiovascular events (death from CAD, non fatal MI, resuscitated cardiac arrest).	No J-curve for the outcome of stroke with SBP. Exponential increase in the risk of primary outcome for BP<110-120/60-70 mmHg.
ONTARGET[23] (2009)	25,588	>55 yrs, CAD, PAD or cerebrovascular disease or DM with organ damage	SBP: 130	Cardiovascular mortality, MI.	J-curve did not occur for stroke. In patients with baseline SBP<130 mmHg, adjusted for covariates, cardiovascular mortality increased with further SBP reduction ($p<0.0001$).
Agarwal R.[39] (2009)	218	Veterans, mean age 68 yrs, men, CKD, 95% under antihypertensive medications	SBP/DBP: 110/70	All-cause mortality.	Monotonic relationship between baseline SBP and DBP and ESRD. J curve was pronounced in patients with advanced CKD, absence of clinical proteinuria or age >65 yrs.
Syst-Eur[58] (2007)	4695	>60 yrs, isolated systolic hypertension	DBP: 70	Cardiovascular events.	J-curve only in patients with coronary heart disease at baseline.
INVEST[19] (2006)	22,576	hypertension, CAD	SBP/DBP: 129/74 (in the adjusted model for time to primary outcome)	All-cause death, nonfatal MI, nonfatal stroke.	Diastolic J-curve was less prominent for patients undergoing revascularisation than those without. Diastolic J-curve was much more pronounced than Systolic J-curve. J-shaped relationship with DBP was observed to a lesser extent for stroke than for MI or mortality.

Kovesdy CP et al.[55] (2006)	860	GFR <60 ml/min/1.73 m^2	SBP/DBP: 133/65	All-cause mortality.	Subgroup analyses based on prevalent CVD status and level of GFR showed that same association was present for both SBP and DBP only in subgroups with GFR≤30 ml/min/1.73 m^2 and for DBP only in the subgroup with CVD.
Botnia Study[53] (2006)	1294	69 yrs, DM	DBP: 75 (with SBP>160) or SBP: 135 (with DBP>90)	All-cause mortality.	U-shaped association between PP and mortality, especially in patients with a positive history of CVD. These observations could be linked to arterial stiffness and heart failure.
IDNT[26] (2005)	1590	30-70 yrs, hypertension, overt diabetic nephropathy	SBP: 120 DBP: 85	Cardiovascular death, CHF. MI, total mortality.	The stroke risk continued to decrease even with DBP<85 mmHg.
VALUE[13] (2004)	15,245	≥50 yrs, treated or untreated hypertension, high-risk for cardiac events	SBP: 120	Cardiovascular events.	The possibility of a J-curve is suggested for BP values close to recommended goals for high-risk patients.
Jafar TH et al. meta-analysis[46] (2003)	1860	Non-diabetic kidney disease	SBP: 110	Kidney disease progression.	SBP<110 mmHg may be associated with higher risk for kidney disease progression.
INDANA meta-analysis[16] (2002)	40,233	hypertension	Untreated subjects: DBP 90 Treated subjects: DBP 84	Total mortality.	J-curve not related to antihypertensive treatment.
			Untreated subjects: DBP 84 Treated subjects: DBP 85	Cardiovascular mortality	
IST[31] (2002)	17,398	Confirmed ischaemic stroke, 81.6% with high BP	SBP: 150	Death within 14 days, death or dependency at 6 months.	Death within 14 days increased by 17.9% for every 10 mmHg below 150 mmHg (p<0.0001). Small number of subjects with SBP<120 mmHg.
			SBP: 120	Recurrence of ischaemic stroke within 14 days.	
SHEP[59] (1999)	4736	≥60 yrs, isolated systolic hypertension	DBP: 70	CVD.	Increased risk for cardiovascular events with DBP<70 mmHg was observed in the treated group of patients.
HOT[11,12] (1998)	18,790	Mean 61.5 yrs, hypertension	DBP: 83	MI.	The findings were observed in the subgroup with ischaemic heart disease. No J-curve for non-ischaemic patients.
FRAMINGHAM[15] (1991)	5209	30-62 yrs, with or without previous MI	DBP: 75-79 (high 70s)	Death from CHD (MI death, death from CHD).	U-shaped relation occurred only for high risk patients (with MI but free of CHF). It existed for both patients given antihypertensive treatment and those not.
Farnett L et al[10] (1991)	48,000	Treated hypertension	DBP: 85	Cardiac events.	Studies did not show consistent J-curve for stroke. Steeper J-curve in older and in patients with pre-existing ischaemic heart disease.
Cruickshank JM. et al[6] (1987)	902	Moderate to severe treated hypertension	DBP: 85-90	MI mortality.	J-curve confined to those with evidence of ischaemic heart disease.
Stewart IM.[5] (1979)	169	Uncomplicated, middle-aged, treated hypertension	DBP: 90	MI.	The findings suggest that BP should seldom be reduced by more than 22%.

CAD – coronary artery disease; CHF – congestive heart failure; CKD – chronic kidney disease; CVD – cardiovascular disease; DBP – diastolic blood pressure; DM – diabetes mellitus; ESRD – end-stage renal disease; GFR – glomerular filtration rate; MI – myocardial infarction; PAD – peripheral artery disease; PP – pulse pressure; SBP – systolic blood pressure

Pathophysiological aspects

As is well known, vital organs such as the heart, brain, and kidneys have a system of autoregulation, which provides them with the ability to preserve tissue perfusion despite substantial changes in BP. However, organs with atherosclerotic vascular disease to some extent lose their ability for autoregulation, since a milder reduction in BP may cause organ hypoperfusion, due to the already stenotic arteries. This mechanism offers an explanation for the J-shaped relationship between BP levels and adverse outcomes, especially observed in high-risk populations. It also explains why in patients free of cardiovascular disease the relationship between BP and cardiovascular event rate is linear down to very low BP levels (110/70). It seems that, since coronary blood flow occurs mainly during diastole, the heart has a system of autoregulation that is more vulnerable to BP changes, especially changes in DBP, than the kidneys or brain.

Moreover, increased arterial stiffness, which is indicated by increased pulse pressure, may constitute an explanatory mechanism for the J-curve phenomenon, particularly for DBP. Studies in elderly subjects or subjects with isolated systolic hypertension have demonstrated a J-curve relation for pulse pressure,[22] or for DBP only when pulse pressure was elevated.[53] This implies that the J-curve phenomenon may be attributable to arterial stiffness, which is an important predictor of adverse outcome, and not to a treatment-induced reduction in DBP levels. Concomitant situations that may increase the prevalence of the J-curve and amplify its consequences are the natural extreme dipping of BP during the night, and orthostatic hypotension.[61]

Another issue is that the J-curve may be explained by the fact that comorbidities (such as heart failure, renal dysfunction, CAD, impaired general health condition) may cause increased mortality, adverse outcomes in atherosclerotic patients, and lower BP levels, rather than the opposite (reverse causality). Among subjects undergoing a first coronary artery bypass graft or percutaneous coronary intervention, a recent study analysed 7180 subjects with chronic CAD.[62] The unadjusted incidence of cardiovascular death was greater for DBP<70 mmHg than for DBP≥70 mmHg, while the incidence of myocardial infarction and stroke was unaffected by DBP levels. However, after adjustment for the other cardiovascular predictive factors (heart failure, left ventricular dysfunction, GFR, prior cardiovascular disease) the hazard ratio for cardiovascular death was similar for the two DBP levels. Along similar lines, a study in elderly patients demonstrated a U-shaped relation between DBP and cardiovascular or total mortality in the untreated group.[63] However, patients in the lowest thirds of the BP range showed greater decreases in body weight and haemoglobin concentration, suggesting general health deterioration.[64] Also, a Finnish study, observing a U-shaped relationship between DBP and total and cardiovascular mortality in 16,913 hypertensive subjects, showed that the complications of hypertension were more important determinants of mortality than was low DBP alone; therefore low DBP was mostly a secondary phenomenon.[65]

Conclusions

The "J-curve issue" remains unresolved since the data are conflicting. Most of the studies advocate a treatment-induced J-shaped relationship between BP and cardiovascular events in hypertensive subjects with a history of cardiovascular disease. Since no benefit seems to accrue from lowering BP to fully normotensive levels, we should avoid aggressive treatment in these subjects. Although studies so far have not confirmed the J-curve with respect to renal outcomes, it seems that lower achieved BP levels to <130/80 mmHg are related to a beneficial renal outcome, mainly in patients with advanced proteinuric nephropathy. Until recently it was believed that there is no J-curve in relation to stroke risk. New data from subjects with a recent ischaemic stroke challenge this statement and support the possible existence of thresholds for SBP below which stroke risk increases. Finally, new prospective randomised trials, such as the SPRINT trial,[66] designed to compare different BP goals and exclude possible confounders, are needed in order to elucidate the J-curve phenomenon. Until then, in all hypertensive subjects, at lower or higher risk, BP goals should be within the range of 130-139/80-85 mmHg.

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