When does low normal blood pressure become too low? The J-curve phenomenon

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Abstract The J-shaped relationship between blood pressure lowering and cardiovascular morbidity and mortality has been the topic of debates in the last three decades, especially because it has been shown that this relationship is not the same in different populations of hypertensive patients. This phenomenon is very important from a clinical point of view because it determines blood pressure cut-off values in patients with different comorbidities (diabetes, coronary artery disease, kidney disease, previous stroke). There is still no consensus about the J-shaped relationship. However, the number of studies supporting the existence of the inverse relationship between blood pressure reduction, especially diastolic pressure lowering, and cardiovascular morbidity and mortality, is increasing each year. The aim of this review is to summarize current knowledge about the J curve in a different population of hypertensive patients.

Keywords *Arterial hypertension – J-curve – blood pressure lowering.*

INTRODUCTION

The reduction of arterial pressure in patients with arterial hypertension (AH) causes prevention and regression of the target organ damage, as well as the reduction of cardiovascular morbidity and mortality. However, the benefit from the greater blood pressure (BP) reduction is uncertain because of the J-curve phenomenon that is defined as the inverse relationship between low BP and cardiovascular morbidity and mortality. After the release of new guidelines of the European Society of Hypertension this year[1], this topic has been actualized, and numerous questions still remain unanswered. According to the previous guidelines, the recommended target value of BP in the general population of AH patients is 140/90 mmHg, whereas in high-risk patients with type 2 diabetes mellitus and/or clinical history of cerebrovascular and coronary events, as well as in patients with evidence of target organ damage, the target BP was 130/80 mmHg[2]. New guidelines state that the BP should be < 140/90 mmHg in all AH patients regardless of comorbidities (previous stroke or transient ischaemic attack, chronic kidney failure). There are only two exceptions: diabetic patients with a target BP < 140/85 mmHg, and elderly hypertensive patients with a recommended systolic BP 140-150 mmHg that is significantly different from the previous guidelines[2].

The J-curve phenomenon was mainly associated with the diastolic BP level[3]. However, it is very difficult to separate the unfavourable influence of a low diastolic BP from the impact of the decreased systolic BP on cardiovascular morbidity and mortality. Thus, recent investigations have studied both the influence of lowering systolic and diastolic BP. Previous studies investigated whether the J-curve phenomenon was limited only to AH patients with coexisting coronary artery disease, cerebrovascular diseases, diabetes or peripheral artery disease.

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THE J-CURVE AND CARDIOVASCULAR EVENTS – THE PATHOPHYSIOLOGICAL BASIS

Coronary circulation is unique in many ways. Unlike other arteries, coronary artery filling occurs during diastole, and when coronary perfusion pressure falls to 40-50 mmHg, diastolic flow in the coronary arteries is impeded[4]. On the other hand, during systole, contraction of the myocardium causes compression of intramyocardial vessels with a consequent reduction of the coronary flow, especially in intramural and epicardial arteries. In the hypertrophic myocardium of AH patients capillary network density is significantly reduced, and autoregulatory mechanisms are compromised, which leads to compromised myocardial perfusion, worsening of myocardial ischaemia with consequent increase in left ventricular filling pressure and decrease of the perfusion gradient.

In AH patients with left ventricular hypertrophy subendocardial ischaemia may occur in the absence of stenosis. A sudden reduction of diastolic BP to values between 85 and 90 mmHg could cause asymptomatic ischaemia[4]. Owens and O'Brien simultaneously recorded arterial BP and ECG during a period of 24 hours, and detected a relationship between myocardial ischaemic episodes and diastolic (rarely systolic) hypotension[5]. Merlo et al. studied the AH treatment in the elderly and found that a reduction in diastolic BP below 90 mmHg significantly increased the risk of ischaemic events[6], confirming the existence and importance of the J-curve phenomenon.

The brain has a similar ability of blood flow autoregulation as the heart. Normally, blood flow occurs efficiently at a mean BP from 60 to 150 mmHg. These values are flexible and strongly influenced by mechanisms that affect the BP level, such as activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS). However, unlike the coronary circulation, which depends on diastolic BP, the cerebral circulation depends on the systolic BP[7]. The possible pathophysiological mechanisms (causes and consequences) describing the J-curve phenomenon in AH are presented in figure 1.

THE J-CURVE IN HYPERTENSIVE PATIENTS WITH CORONARY ARTERY DISEASE

In 1979 Stewart was the first researcher who found that the reduction of diastolic BP below 90 mmHg increased the risk of myocardial infarction fivefold compared with diastolic BP between 100 to 109 mmHg[8]. A few years later, Cruickshank et al. analysed the impact of diastolic BP between 85 and 90 mmHg on the development of acute myocardial infarction and revealed that the J-curve phenomenon was limited to the patients with established coronary artery disease[9]. Samuelsson et al. did not find an additional benefit from the reduction of BP below 150/85 mmHg in a population of middle-aged men[10]. The research, following untreated AH patients

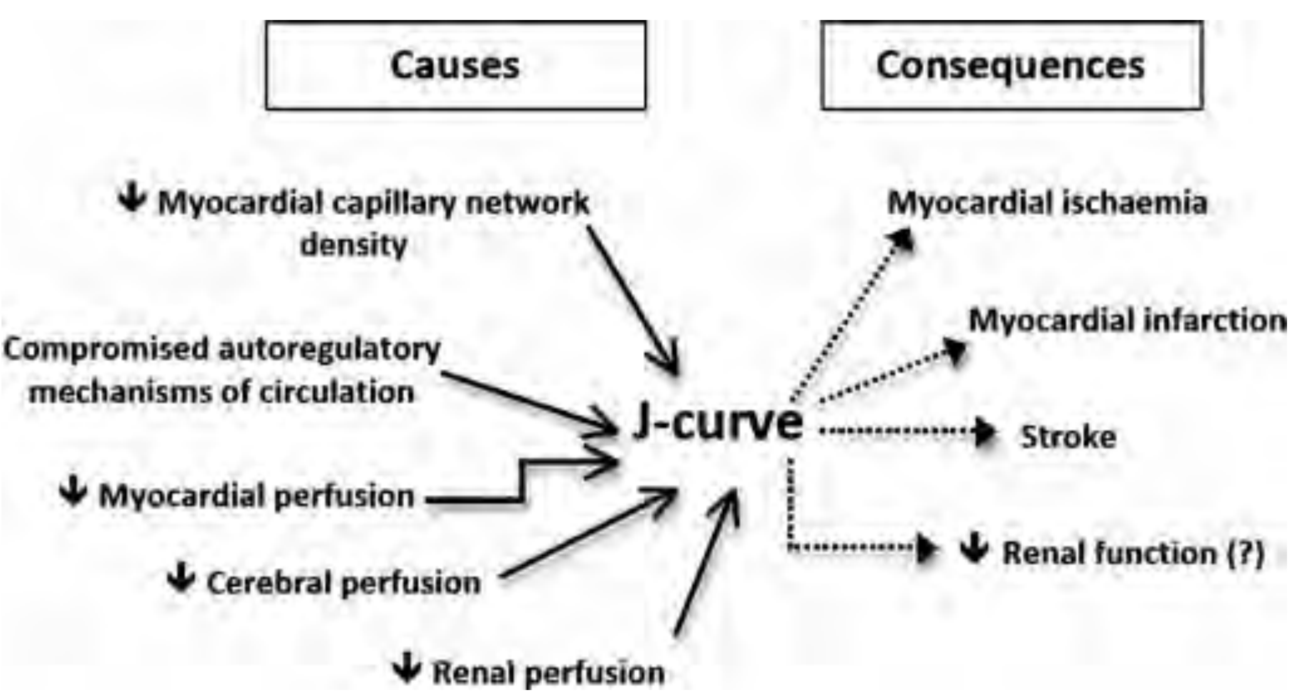

Fig. 1 The possible pathophysiological mechanisms (causes and consequences) describing the J-curve phenomenon in arterial hypertension.

during four years, demonstrated the increased incidence of fatal and non-fatal myocardial infarction in the patients with minor (< 6 mmHg) and major (> 18 mmHg) reduction in diastolic BP, whereas the reduction of 7 to 17 mmHg was associated with a low risk of acute coronary events[11]. A meta-analysis of the large studies investigating the AH treatment, detected a J-shaped relationship between coronary events and diastolic BP, but not between systolic BP and stroke[12]. The J-shaped relationship between systolic and diastolic BP and cardiovascular events has been confirmed in large studies (see table 1).

Table 1 The basic characteristics of studies that proved the J-shaped relation between blood pressure and cardiovascular morbidity and mortality.

Reference	Sample size and subjects included in the study	J-curve point (mmHg)	Events associated in J-shaped mode with BP and other findings
J curve in hypertensive disease with coronary artery disease			
Framingham study[13]	5,209 patients, 30 -62 years old, with or without previous MI	DBP: 75-79	J-shaped relationship was found between DBP and heart failure and myocardial infarction. It was detected in all patients (with and without antihypertensive therapy).
HOT[14]	3,080 high-risk hypertensive patients	DBP: 80	J-shaped relationship was found only between DBP and myocardial infarction.
INVEST[15]	22,576 hypertensive patients with coronary artery disease ≥ 50 years old	SBP/DBP: 129/74	J-shaped relationship was revealed between SBP and DBP and all-cause mortality, nonfatal myocardial infarction and nonfatal stroke. DBP J-curve was much more prominent than SBP J-curve.
ACTION[16]	7,665 patients with concurrent stable angina and hypertension	-	J curve was found between DBP and cardiovascular events, but no among DBP and stroke.
VALUE[17]	15,245 hypertensive patients ≥ 50 years old, treated or untreated for hypertension	SBP: 120	J curve was detected between SBP and cardiovascular events.
ONTARGET[18]	25,588 high-risk patients > 55 years old with coronary or peripheral artery disease, or cerebrovascular disease or diabetes with organ damage	SBP: 130	J-shaped relation was found between SBP and cardiovascular mortality and myocardial infarction, but it was not confirmed for stroke.
TNT[19]	10,001 patients 35 -75 years old with coronary artery disease and LDL < 3.36 mmol/l	SBP/DBP: 146.3/81.4	J curve was detected among SBP and DBP and cardiovascular mortality, non-fatal myocardial infarction and resuscitated cardiac arrest. J curve was not found between SBP and stroke.
PROVE – IT TIMI[20]	4,162 patients with acute coronary syndrome	SBP/DBP: 110/70	J-shaped relationship was found between SBP and DBP and all-cause mortality, myocardial infarction, unstable angina, revascularisation after 30 days and stroke.
J curve in diabetes			
ACCORD-BP[30]	4,733 participants with type 2 diabetes	SBP: 120	SBP < 120 mm Hg did not reduce the rate fatal and non-fatal major cardiovascular events in comparison with SBP < 140 mmHg.
Vamos et al.[31]	126,092 adults with a new diagnosis of type 2 diabetes	SBP/DBP: 110/70	BP < 130/80 mm Hg was not associated with reduced risk of all cause mortality. BP < 110/75 mm Hg was associated with an increased risk for adverse outcomes.
ROADMAP[32]	4,447 patients aged 18-75 with type 2 diabetes	SBP: 120	J curve was found between SBP and cardiovascular mortality.
INVEST subanalysis[33]	6,400 patients with coronary artery disease, diabetes and hypertension	SBP: 115	J-shaped relationship was detected between SBP and all-cause mortality, especially when SPB < 115 mmHg.
J curve and stroke			
IST[35]	17,398 mostly hypertensive patients with confirmed ischaemic stroke	SBP: 150	J curve was found in relation between SBP and mortality within 14 days or 6 months. Mortality in the first 2 weeks increased by 17.9% for every 10 mm Hg below 150 mm Hg.
J curve in the elderly			
EPESE[44]	14,000 pubjects ≥ 65 years of age	SBP: 130	J-shaped relationship was revealed between SBP and total mortality
SHEP[45]	4,736 patients older than 60 years with isolated systolic hypertension	DBP: 70	J curve was established between DBP and cardiovascular events.

SBP: systolic blood pressure, DBP: diastolic blood pressure, LDL: low-density lipoproteins.
ACCORD-BP: Action to Control Cardiovascular Risk In Diabetes – Blood Pressure arm, ACTION: A Coronary disease Trial Investigating outcome with Nifedipine, HOT: the Hypertension Optimal Treatment, EPESE: Established Populations for Epidemiologic Studies of the Elderly study, INVEST: the International Verapamil-Trandolapril Study, IST: International Stroke Trial, ONTARGET: Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial, PROVE – IT TIMI: PRavastatin Or atorVastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction study, ROADMAP: Randomized Olmesartan and Diabetes Microalbuminuria Prevention study, SHEP: Systolic Hypertension in The Elderly Program study, TNT: Treating to New Targets study, VALUE: Valsartan Antihypertensive Long-term Use Evaluation study.

In the Framingham study the authors found the J-shaped relationship between the diastolic BP and cardiac death in the patients with acute myocardial infarction independently of the left ventricular function and antihypertensive treatment[13]. In the HOT study, investigators found that a diastolic BP of 82.6 mmHg was associated with the lowest risk of cardiovascular events. The additional reduction of the diastolic BP had no effect on decreasing the risk of cardiovascular complications[14]. A further analysis confirmed the existence of the J-curve relation between the increased risk of coronary artery disease and diastolic BP < 80 mmHg.

The INVEST study yielded the most data about the J-curve and AH[15]. The J-shaped relation was found between systolic BP (< 119 mmHg) and diastolic BP (< 84 mmHg) on the one side, and total mortality and acute myocardial infarction incidence, on the other side. It was detected that the risk of death and non-fatal myocardial infarction was doubled in the patients with a diastolic pressure < 70 mmHg and quadrupled when diastolic BP was < 60 mmHg. A relation between low diastolic BP and risk of stroke was not found. Lubsen et al. in the ACTION study compared normotensive subjects and treated hypertensive patients with stable angina, and detected the J-curve phenomenon for diastolic BP in both groups of patients[16].

The reduction of cardiovascular risk, in the VALUE study which included high-risk patients with untreated hypertension older than 50 years of age, was achieved in patients with a systolic BP between 120 to 130 mmHg, whereas additional decrease of BP was associated with cardiovascular complications[17] (table 1). Similar results were obtained in the ONTARGET study, which also included high-risk patients[18]. The authors found that the significant reduction in systolic BP (< 130 mmHg) was associated with a higher risk of cardiovascular mortality, and acute myocardial infarction with systolic BP < 126 mmHg. The authors revealed that a diastolic BP ≤ 72 mmHg was associated with the higher risk of cardiovascular and cerebrovascular events. The patients with BP reduction (< 140/90 mmHg) demonstrated a significantly lower incidence of complications (cardiovascular and renal disease, stroke) than the patients with stricter BP regulation (< 130/80 mmHg). The J-shaped relationship between the reduction of systolic BP and the stroke incidence was not noticed.

The TNT study revealed the significant correlation between cardiovascular events (total mortality, cardiovascular mortality, non-fatal myocardial infarction and stroke) and diastolic BP < 79.8 mmHg, and systolic BP < 140 mmHg[19]. The subanalysis of the results demonstrated that the patients with coronary artery disease and a systolic BP < 110-120 mmHg and a diastolic BP < 60-70 mmHg had an increased risk of cardiovascular events (but not stroke) in comparison with those with a systolic BP < 146.3 mmHg and a diastolic BP < 81.4 mmHg[20]. The follow-up of patients who were included in the PROVE IT-TIMI study demonstrated that the patients with previous coronary events and a BP equal to 136/85 mmHg had a lower incidence of death from any cause, myocardial infarction, unstable angina, and stroke. The investigators found that a BP < 110/70 mmHg was unsafe for the patients with a previous coronary event[21]. The results of the recently published SMART study confirmed the J-shaped relationship between the mean values of systolic/diastolic BP of 143/82 mmHg and vascular events in the patients with vascular disease during a five-year follow-up[22].

However, the existence of the J-shaped relationship between BP values and cardiovascular mortality and morbidity was not unreservedly accepted[23,24]. Psaty et al. in the Cardiovascular Health Study, including 5,888 adults ≥ 65 years without previous myocardial infarction, heart failure or stroke, did not find a J-shaped relationship between BP level and cardiovascular disease risk, regardless of the fact that the authors found a strong relationship between systolic, diastolic and pulse pressure, with the risk of myocardial infarction and stroke[23]. Additionally, systolic BP was a better predictor of cardiovascular events than diastolic and pulse pressure[23]. Glynn et al. used two studies, including only the participants without prior cardiovascular event: the Physicians' Health Study (17,862 men) and the Women's Health Study (36,944 women), in order to make gender-specific predictive models[24]. The authors failed to demonstrate the J-shaped relation between BP and cardio- or cerebrovascular events. The reason of these results could be the fact that the patients recruited for these studies were in good health, free of previous cardio- or cerebrovascular events, unlike other studies including patients with prevalent heart disease[15-20]. The other possible cause of these results could be the low prevalence of risk factors including hypertension, diabetes, obesity and cigarette smoking in these populations[24].

In the updated European recommendations from 2009, the target BP value in the high-risk group of patients with coronary artery disease was 130-139 mmHg for the systolic BP and 80-85 mmHg for the diastolic BP[25]. However, considering the fact that the target BP lower than 130 mmHg is very difficult to achieve, even after intensive treatment, and findings which revealed that there is no significant reduction in hard CV outcomes after this reduction[26,27], the new guidelines are not so strict, and tolerate BP up to 140/90 mmHg in these patients.

THE J CURVE IN PATIENTS WITH HYPERTENSION AND DIABETES

In the previous European guidelines from 2007, the target BP in AH patients with diabetes is 130/80 mmHg[2], whereas in the new recommendations the target BP value is < 140/85 mmHg[1]. This value was based on the results of previous investigations (table 1). The UKPDS study showed that aggressive BP control with a target BP of 144/82 mmHg reduced the macro- and microvascular complications[28]. Additionally, the ABCD study showed that systolic BP < 132 mmHg did not significantly reduce cardiovascular risk in comparison with systolic BP < 138 mmHg[29]. The ACCORD-BP study compared the intensive antihypertensive treatment with the standard treatment in high-risk patients with diabetes mellitus and a concomitant cardiovascular risk factor (atherosclerosis, microalbuminuria, left ventricular hypertrophy), or with at least two other risk factors[30]. After a year, there was no difference in the risk of non-fatal heart attack, stroke and cardiovascular death between the two groups[30]. However, the incidence of stroke was significantly lower in the intensively treated group that also suffered more side effects of the treatments. The researchers from the large observational study conducted in the United Kingdom concluded that systolic BP in diabetic patients should be reduced to 130-139 mmHg, whereas diastolic BP should be decreased to 80 - 85 mmHg[31].

The ROADMAP study, including patients with type 2 diabetes aged 18-75 y, showed a J-shaped relationship between systolic BP and cardiovascular mortality[32]. The substudy of the INVEST trial, which included hypertensive patients > 50 years old with coronary artery disease and diabetes, also revealed a J-curve relation between systolic BP and all-cause mortality[33].

THE RISK OF STROKE DEPENDING ON THE LEVEL OF SYSTOLIC AND DIASTOLIC BLOOD PRESSURE

BP reduction in AH patients is essential for the primary prevention of cerebrovascular disease. The meta-analysis, including 73,913 high-risk patients with diabetes, showed that intensive antihypertensive treatment with target BP values < 130/80 mmHg caused a reduction of the stroke risk by 39% [34]. Additionally, a reduction of systolic BP of 5 mmHg reduced the risk of stroke by 13%, and a decrease in diastolic BP of 2 mmHg reduced this risk by 11%. The ONTARGET and TNT studies (table 1), which included patients with no symptoms, did not show the J-shaped relationship between BP and the risk of stroke[18,20]. The authors concluded that *"the lower the better"* rule is valid for the prevention of stroke, even when systolic BP < 110 mmHg of pressure[18]. Based on these results, it could be hypothesized that cerebral autoregulation is more effective than cardiac because it managed to maintain blood circulation and tissue perfusion in the conditions of the decreased BP.

Data on optimal BP values in the secondary prevention of stroke are scarce. In the IST study, investigators demonstrated the association between a systolic BP < 120 mmHg in patients with ischaemic stroke and an increased risk of another stroke within two weeks from the first stroke[35] (table 1). In the post-hoc analysis of the multicentre observational study that involved 20,330 patients over 50 years of age with recent non-cardioembolic stroke, investigators showed that the risk of stroke recurrence was higher in the patients with low, high and very high systolic BP. These findings mostly support the hypothesis that optimal systolic BP in the secondary prevention of stroke ranged from 120 to 139 mmHg[36]. The mortality in the first two weeks increased by 17.9% for every 10 mmHg below 150 mmHg.

On the other hand, Yusuf et al. who included 20,332 patients with recent ischaemic stroke did not find differences in the outcome between the groups with systolic BP equal to 136 vs. 140 mmHg[37]. The lack of data that could strongly support the lower target BP in the patients with previous stroke resulted with the same BP target value as for other high-risk patients in the new guidelines[37].

PERIPHERAL ARTERY DISEASE AND J CURVE

Although studies confirmed AH as a predictor of peripheral artery disease (PAD), the BP target value and choice of antihypertensive drugs in these patients, as well as in patients with carotid and renal artery disease are unknown[38,39]. Mehler et al. found that intensive BP lowering to a mean of 128/75 mmHg resulted in a significant reduction in cardiovascular events in patients with PAD and diabetes[40], whereas the ABCD trial revealed that aggressive BP treatment in the PAD patients was effective in reducing the risk of cardiovascular events[29].

The data about the BP target value in patients with carotid artery disease are even more scarce. The SANDS trial, which investigated the influence of conventional and strict control of LDL cholesterol and BP in patients with type 2 diabetes, found that aggressive antilipid and antihypertensive treatment resulted in a greater regression of carotid intima-media thickness than the standard treatment[41]. Interestingly, the decrease in carotid intima-media thickness was significantly related to the decrease in LDL cholesterol, but not to the decrease in systolic BP, when both factors were combined in a model. On the other hand, reduction in left ventricular mass was significantly related to the decrease in systolic BP, but not to the LDL cholesterol decrease[41].

To our knowledge, there is no study that investigated target BP value in individuals with renal artery disease, even though AH is considered one of the most important predictors of atherosclerotic renovascular disease[42]. Considering the fact that renal perfusion occurs mostly during systole, it does not seem that the J-curve phenomenon, at least for diastolic BP, could be relevant for renal outcomes. However, studies demonstrated that lowering BP levels to < 130/80 mmHg was related to a favourable renal outcome mostly in the patients with advanced proteinuria, but not for all patients with chronic kidney disease[43].

THE J-CURVE PHENOMENON IN THE ELDERLY

The new guidelines brought most innovations in this group of patients since they recommend that the elderly should have a systolic BP between 140 and 150 mmHg, whereas a systolic BP lower than 140 mmHg should be considered only for the fit elderly patients[1]. Diastolic BP in any case should be lower than 90 mmHg[1].

AH in the elderly is a specific topic due to chronic diseases such as neoplasms, chronic infections, malnutrition, left ventricular dysfunction of different origin, which could significantly aggravate the BP control. The EPESE study investigated the relation between AH and mortality in the elderly, and revealed a J-shaped relationship between systolic BP and total mortality[44] (table 1). It was concluded that overall and cardiovascular mortality were increased in patients with a low diastolic BP (< 75 mmHg).

AH is very frequent in this population, especially the isolated systolic form that is related to the increased pulse pressure. Under these circumstances medical treatment of AH necessarily causes undesirable reduction in diastolic BP. The SHEP study demonstrated that the reduction of diastolic BP to 70 mmHg increases the risk of cardiovascular events, whereas the reduction of BP to 55 mmHg doubles that risk[45]. The treatment of this form of AH is a major challenge because the parallel reduction of systolic and diastolic BP maintains high pulse pressure that is a powerful independent predictor of cardiovascular events, particularly myocardial infarction.

The HYVET study did not show the J-shaped relation between systolic and diastolic BP and the risk of coronary or cerebrovascular events[46]. A possible explanation for this finding is the study population that included healthy elderly subjects, which is probably the reason why adverse effects of diastolic BP reduction were not detected. However, the target systolic BP was < 150 mmHg.

The VALISH study concluded that the standard control of systolic BP (< 140 mmHg) was safe for healthy elderly patients over 70 years of age, but there was no benefit in preventing cardiovascular events compared with the less strict BP control (140-150 mmHg)[47]. This finding represents very good news for clinicians because it is very difficult to achieve a systolic BP ≤ 140 mmHg in patients with isolated systolic hypertension. Furthermore, these studies showed that only fit elderly patients, who are rarely seen in everyday clinical life, will have a benefit from BP reduction under 140/90 mmHg.

Protogerou et al. excluded the existence of the J-shaped relation between systolic BP and cardiovascular mortality. However, the authors discovered that the relation between diastolic BP and cardiovascular disease is not linear but has a J-shaped form with a cut-off value of 60 mmHg[48]. At the same time the investigators concluded that the association of low diastolic BP and cardiovascular mortality is not a simple epiphenomenon due to age-associated chronic diseases, increased aortic stiffness, heart failure, or decreased peripheral vascular resistance, but it could also deteriorate coronary perfusion with aggressive BP reduction.

All these studies were the reason why authors of recommendations decided to increase the cut-off value for BP to 140-150/90 mmHg in the elderly hypertensives[1], which appears to be far more logical and reasonable than previous target values in this population[2].

HOW TO OVERCOME THE PROBLEM?

Taking into consideration the strength of the evidence on the impact of diastolic BP reduction on the increased risk of cardiovascular morbidity and mortality in high-risk patients with coronary artery disease and isolated systolic AH, it would be helpful to try to predict possible adverse events and adjust the antihypertensive treatment. A BP pattern, especially an extreme dipping pattern, determined by 24-hour BP monitoring may help physicians to predict the risk. The unfavourable BP patterns (non-dipping, reverse dipping and extreme dipping) are associated with the organ damage, the number of episodes of myocardial ischaemia and stroke[3,49]. In addition, orthostatic hypotension, easily detected by measuring the pressure in the standing and sitting position, increases the prevalence and consequences of the J curve.

With respect to the medical treatment, drugs that slow the heart rate have an advantage due to prolonging diastolic perfusion of the coronary vascular bed. This refers to beta blockers and non-dihydropyridine calcium channel blockers. Drugs that increase the heart rate may have an adverse effect on coronary perfusion, and therefore, short-acting calcium channel blockers and vasodilators (such as hydralazine) should be avoided. Considering the fact that left ventricular hypertrophy has been listed as one of the possible preconditions for potential adverse effects of low diastolic BP, the treatment with RAAS blockers and calcium channel blockers should be used due to the favourable effects of these drugs on myocardial hypertrophy regression. The RAAS blockers and calcium channel blockers, and possibly diuretics, have an advantage in the treatment of patients with isolated systolic AH because of the positive influence of these drugs on artery compliance, and a significant reduction in systolic, less diastolic BP, which is very important in these patients.

CONCLUSION

Although in clinical practice we are trying to achieve BP values close to 140/90 mmHg, and fail in many cases due to various reasons, the J-curve phenomenon is very interesting and mainly refers to high-risk patients with coronary artery disease, stroke, diabetes, and a population of elderly patients. The target BP < 130/80 mmHg in patients with diabetes and previous cardiovascular events, specified in the recommendations from 2007, has not been confirmed by the results of the latest research, which is why the new guidelines changed the target values for these groups of patients. The J-shaped relationship between diastolic BP and cardiovascular morbidity and mortality could be found in patients with coronary artery disease and isolated AH. However, as the new guidelines stated, the investigations which studied this phenomenon have several limitations: (i) most of the studies are randomized trials, not observational studies; (ii) the numbers of patients and events in the lowest BP groups are small and those patients mostly have an increased baseline risk, and above all, (iii) the nadir values of systolic and diastolic BP are very different between the studies. However, the J-curve phenomenon is an important topic because it has a logical pathophysiologic explanation, which is why it should be studied in an appropriately designed investigation with a great number of patients in all BP groups after which we could make a definite conclusion.

CONFLICT OF INTEREST: none.

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