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Revisiting the J-curve Phenomenon. An Old New Concept?

Daniel Medeiros Moreira[1,3,*], Milton Ricardo Poffo[1], Ramsés Miotto[1], Sulyane Matos De Menezes Alves[1], Ademilson Rogerio Ferreira[1] and Erlon Oliveira de Abreu-Silva[2]

[1]Santa Catarina Institute of Cardiology - ICSC, Sao Jose, Brazil; [2]Division of Interventional Cardiology, Federal University of Sao Paulo and Kidney Hospital; Sao Paulo, Brazil; [3]Rio Grande do Sul Institute of Cardiology - IC/FUC, Porto Alegre, Brazil

Abstract: Cohort studies have demonstrated the association between blood pressure and increased cardiovascular events. There are different therapeutic strategies to achieve goals of systolic and diastolic blood pressure. For a long time, therapeutic targets were not well defined and the concept of "smaller is better" was used diffusely. However, clinical trials have shown the presence of a "J-curve" in different clinical situations: below a certain level of blood pressure, more aggressive reductions may not represent benefit and increase the incidence of adverse events in elderly patients, patients with coronary artery disease, patients with diabetes or chronic renal failure.

Keywords: Cardiovascular disease, cardiovascular risk, blood pressure, hypertension, hypertension treatment, j-curve.

INTRODUCTION

U.S. data shows that 1 in 3 adults have hypertension (HTN) [1]. Hypertension is responsible for an attributable population risk of 17.9% for acute myocardial infarction and can reach 84.9% for ischemic stroke [1-3].

The first attempts to measures the blood pressure date back to the experiments of Stephen Hales on horses, published in 1733, however non-invasive blood pressure measurement in humans began in the second half of the nineteenth century [4]. Until the first decades of the twentieth century, however, though admittedly associated with injury to target organs, HTN was considered in many cases as a "compensatory" response that did not require treatment [5]. After the data from the Framingham Study and some clinical trials of antihypertensive drugs, the association between HTN and cardiovascular disease became clearer, as well as the need for antihypertensive treatment [6, 7].

In the late 70s some authors indicated that aggressive blood pressure reduction could have negative effects, suggesting the presence of the effect called "J-curve": a bimodal imaging, where reduction of cardiovascular events is directly proportional to the decrease in pressure levels up to a theoretical threshold or nadir and beyond these levels, there is an increased risk of cardiovascular complications [8]. Some clinical trials, however, showed that a substantial reduction in blood pressure could bring additional benefits, the concept of "smaller is better" [9].

*Address correspondence to this author at the Instituto de Cardiologia de Santa Catarina - Rua Adolfo Donato, SN, São José-SC, Brazil, CEP 88103-901; Tel: +55 (48) 84175590; E-mail: danielmedeirosmoreira@gmail.com

Nowadays, new evidence again demonstrates the existence of a J-curve in antihypertensive treatment in different situations, such as diabetes, coronary artery disease and renal failure [10-12]. These findings began to influence new guidelines, which came to reevaluate therapeutic targets [13].

Given these facts, this paper reviews concepts related to the J-curve, and its therapeutic implications.

ANTIHYPERTENSIVE TREATMENT IN YOUNG PATIENTS WITHOUT COMORBIDITIES

Despite HTN being an independent risk factor for cardiovascular events, there are few studies that assess the existence of a J-curve pattern in a hypertensive population free of other comorbidities.

At the end of the 60s, data from the Framingham study showed that patients with the lowest quintiles of systolic and diastolic blood pressure showed a lower incidence of coronary artery disease [6]. Reviews of the National Health and Nutrition Examination Survey Epidemiologic Follow-up Study (NHEFS) cohort demonstrated that even in patients without coronary disease with systolic blood pressure (SBP) between 130 and 139mmHg or diastolic blood pressure (DBP) between 85 and 89mmHg, the number needed to treat is 25 to prevent one case of coronary artery disease with a reduction in systolic pressure of 12 mmHg [14]. Clinical trials, however, showed no benefit with an aggressive reduction of blood pressure: the Behandla Blodtryck Bättre (swedish for Treat Blood Pressure Better - BBB) study showed that intensive lowering of DBP was safe despite not reducing the incidence of cardiovascular events in patients with less than 80 mmHg levels [15]. The Hypertension

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Optimal Treatment (HOT) trial, that randomized 18,790 hypertensive patients with a mean age of 61 years also showed no evidence of J-curve phenomenon among nonischemic patients: there is a benefit in reducing SBP to 140 mmHg and DBP to 85 mmHg, however additional reductions in SBP to 120 mmHg and DBP to 70 mmHg showed no additional risk or clinical benefit [9]. Likewise, a large meta-analysis of hypertensive adults with no history of vascular disease, concluded that there is an association between systolic or diastolic blood pressure and increased vascular events: a reduction in blood pressure to the threshold of 115 mmHg for SBP and / or DBP 75 mmHg promoted a reduction the incidence of vascular events, however the reduction below this levels did not bring evidence of protection or additional risk [16].

There is little evidence that there may be a negative effect of more aggressive blood pressure reductions. One such evidence was presented the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial, that found a lower risk of cardiovascular events in a level of SBP around 120-130 mmHg, but higher reductions were associated with a significant increase in cardiovascular complications [17]. The Individual Data Analysis of Antihypertensive Intervention (INDANA) project steering committee published a meta-analysis showing the presence of J-curve phenomenon in patients receiving antihypertensive (DBP reduction to 80 mmHg) and in patients who received placebo (reduction in DBP to 85 mmHg). This finding suggests that the J-curve cannot be related to drug DBP reduction but to a phenomenon of reverse causality given that patients encompassed in the lower pressure range also have poorer health [18].

Within the set of current evidence, there is not a clear presence of the J-curve phenomenon among hypertensive patients without other comorbidities. Thus, recent guidelines set a therapeutic target of SBP below 140mmHg and DBP below 90mmHg for patients under 60 years old [13] or under 80 [19].

J CURVE IN THE ELDERLY

At the end of the 80s, evidence showed that patients 60 years old or older who receive antihypertensive treatment had a higher mortality rate in the lowest tertiles of systolic and diastolic blood pressure [20]. Reviews of patients over 55 years of the Rotterdam study showed, at the end of the 90s, that higher levels of SBP and DBP are associated with an increased incidence of stroke. It was also demonstrated, however, that lower levels of DBP have a significantly higher incidence of stroke, clearly showing a J-curve for DBP [21]. The Hypertension in the Very Elderly Trial (HYVET), in turn, demonstrated that even in patients older than 80 years old, blood pressure control was important and promotes the reduction of cardiovascular events, including reduction of deaths from any cause. This study, however, had an important limitation as a therapeutic SBP target of 150mmHg and DBP target of 80mmHg and did not allow us to conclude that more aggressive reductions could bring greater benefit [22]. Recent meta-analysis also demonstrated benefits of a reduction with the same therapeutic targets; however the reduction in DBP was inversely associated with cardiovascular mortality and the incidence of stroke [23]. The Japanese trial to assess optimal systolic blood pressure in elderly hypertensive patients (JATOS) study, in turn, evaluated a Japanese population aged 65 years old and showed that a SBP below 140mmHg was not better than a target between 140 and 160mmHg when assessed the incidence of cardiovascular disease, cerebrovascular or renal disease were assessed [24]. The Valsartan in Elderly Isolated Systolic Hypertension Study (VALISH) study that evaluated patients aged 70 years old or more, corroborated data of JATOS study and demonstrated that reductions in SBP below 140mmHg compared to a target between 140 to 150mm Hg did not reduce the incidence of a combined endpoint of sudden death, stroke, myocardial infarction, death from heart failure or other cardiovascular causes, hospitalization for cardiovascular causes or renal failure [25]. Thus, it becomes clear that elderly patients benefit from reductions in SBP below 160mmHg levels, however there is no adequate evidence to pinpoint which would be ideal for SBP target [26].

One possible hypothesis for increased morbidity and mortality in some studies could be an increase in fractures after falls in the elderly patients with more stringent blood pressure control. A recent cohort study showed, however, that despite antihypertensive treatment increases the risk of fractures from falls, there is no linear relationship with blood pressure reduction or the number of antihypertensive drugs used [27].

Given the current evidence, the recommendations of the guidelines no longer recommend aggressive blood pressure reductions in patients aged over 60 years old, and began to admit more complacent therapeutic target, as SBP of less than 150mmHg and DBP of less than 90mmHg [13, 19, 28].

J-CURVE IN PATIENTS WITH DIABETES MELLITUS

Hypertension is commonly found in diabetic patients and appropriate treatment should be carried out carefully, since the two factors multiply cardiovascular risks that each one would have alone [29]. It is known, for instance, that for every 10mmHg reduction in SBP, there is a 15% reduction in the risk of death, as well as reducing the risk of secondary complications related to diabetes [30].

In the late 90s some studies proved the importance of aggressive treatment of blood pressure, aiming to reduce the risk of cardiovascular events: in the UK prospective diabetes study (UKPDS), treatment with angiotensin converting enzyme inhibitors or angiotensin receptor blockers in order to reduce blood pressure to below 150/80mmHg levels substantially decreased the risk of death and diabetes-related complications [31]; An analysis of the HOT study, that evaluated patients with diabetes, also demonstrated reductions in cardiovascular events in type 2 diabetic patients who received more aggressive antihypertensive therapy. However, both studies had high average levels of SBP (approximately 144 mmHg)

[9, 31]. These and other evidences were translated into different guidelines [28, 29, 32-34].

In recent decades, however, new evidence emerged and began to counter the paradigm of "smaller is better" in diabetes: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial showed that in diabetic patients, reductions in SBP to below 120mmHg values were not better than the therapeutic SBP target of less than 140mmHg in the incidence of major cardiovascular events or all-cause mortality, and increase the incidence of side effects attributed to antihypertensive medication [10]. The International Verapamil SR-Trandolapril Study (INVEST) also reported no benefit in lowering SBP below 130mmHg in patients with diabetes and suggested, in these cases, to keep SBP between 130 and 139mmHg [35]. Another study, conducted in the UK, found that levels of blood pressure of less than 120/75mmHg in the first year of diagnosis of type 2 diabetes showed a significant increased risk of death, fact that was not observed with blood pressure below 130/80 mmHg [36]. The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) also suggests that antihypertensive treatment should be implemented with caution when SBP meet next 130mmHg or DBP less than or equal to 67 mmHg, due to the possible increase in the incidence of cardiovascular complications events [37].

Although ACCORD as well as ONTARGET studies showed more cardiovascular events with smaller blood pressure levels, they also showed a reduction in the incidence of stroke in diabetic patients with a more aggressive blood pressure control. The first one reports that to prevent one stroke over 5 years it is necessary to refer 89 patients to aggressive blood pressure treatment goals with SBP less than 120mmHg [10]. The second shows that reducing SBP below 130-142 mmHg, achieving levels of 115 mmHg, offers greater protection against stroke [37]. So, when it comes to prevention of cerebrovascular disease, it seems that there is not a J-curve in the treatment of blood pressure in patients with diabetes.

Given the evidence of increased incidence of cardiovascular events and mortality in strict blood pressure control in patients with diabetes, the guidelines have become more permissive: the recommendations of the American Diabetes Association started to suggest that diabetic patients with blood pressure higher or equal to 140/80 mmHg should receive drug treatment, with a target pressure below 140/80 mmHg [38]. The members of the JNC-8, in turn, began to suggest that antihypertensive treatment in diabetic patients to maintain SBP below 140mmHg and DBP between 80-85 mmHg, since there is no proven benefit with more intensive blood pressure control [13]. Moreover, the European Society of hypertension does not clarify “how much” lower than of 140 mmHg should be optimal for SBP [19].

J CURVE IN PATIENTS WITH CORONARY ARTERY DISEASE

The association of hypertension and coronary artery disease (CAD) is clearly demonstrated, regardless of age [39]. It is believed, however, that excessive reduction of DBP as well as elevated blood pressure, increased risk of cardiovascular events in patients with CAD following a bimodal distribution resulting from a J-shaped curve [9-11, 39-43].

The presence of a J-curve in the treatment of patients with CAD has been known for a long time: studies from the 80s already showed a higher cardiovascular mortality in ischemic patients with DBP less than 85mmHg, which did not occur in non-ischemic patients [40]. The main reason for this difference would be the inadequate coronary perfusion: perfusion occurs mainly during diastole and diastolic hypotension could lead to coronary hypoperfusion in patients with impaired coronary flow reserve [11, 41]. The ONTARGET study, however, identified this relationship for both SBP and DBP [44]. Moreover, an analysis of the Pravastatin or atorvastatin evaluation and infection therapy-thrombolysis in myocardial infarction (PROVE IT-TIMI) 22 trial (PROVE-IT TIMI 22) showed that patients after acute coronary syndromes had higher risk of new cardiovascular events with blood pressure values of less than 110/70 mmHg and decreased risk with the blood pressure nearly of 136/85 mmHg [42]. An analysis of the Treating to new targets (TNT) trial of patients with coronary artery disease showed a lower incidence of cardiovascular events with blood pressure around 146.3/81.4mmHg and an increased risk when blood pressure was less than 120/70mmHg [41]. Cohort studies with patients with CAD also suggest that there is an increased risk of cardiovascular events in patients with blood pressure above and below the nadir of 143/82mmHg [45].

There is little evidence to suggest that an aggressive reduction could be beneficial in patients with CAD: the Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis (CAMELOT) study showed that patients with established CAD and normal blood pressure (DBP of less than 100mmHg, with an average of 129/78mmHg), showed a reduction of 31% in the risk of cardiovascular events with the combination of amlodipine. This benefit, however, was not observed with enalapril [46].

Although several sources of data suggest damage of an aggressive reduction of blood pressure, the JNC-7 suggested that there would be no definitive evidence of increased risk, unless the DBP was reduced to values lower than 55 or 60mmHg with treatment. Most recent guidelines, however, suggest that the blood pressure of patients with CAD should be maintained at levels lower than 140/90mmHg, despite not mentioning what are the safe levels of reduction are [13,19].

J CURVE IN PATIENTS WITH CEREBROVASCULAR DISEASE

As in CAD, hypertension is a major risk factor for cerebrovascular disease and antihypertensive treatment is essential in primary and secondary prevention [47].

In the early 90s, evidence pointed to a possible presence of the J-curve effect among patients with established cerebrovascular disease: among patients with stroke or

transient ischemic stroke, SBP levels greater than or equal to 150mmHg showed a significant increase in recurrence of cerebrovascular events compared with patients with lower pressure. Although SBP levels did not confer additional risk, patients with DBP of less than 80 mmHg or greater than 95mmHg were those with higher risk of recurrence [48].

Some other studies, however, showed that DBP even lower than 80mmHg can bring benefits to this patient profile [49]. The Perindopril protection against recurrent stroke study (PROGRESS), meanwhile, compared the combination of perindopril and indapamide with placebo and demonstrated a 28% reduction in the incidence of new strokes with an average SBP reduction of 90 mmHg and a DBP reduction of 40 mmHg in patients with or without HTN [50].

Although there is also no clear evidence about the presence of a J-curve in cerebrovascular disease, there are also no evidence or recommendations that SBP should be reduced to levels below 130mmHg [19].

J CURVE IN PATIENTS WITH CHRONIC KIDNEY DISEASE

In patients with chronic kidney disease, the main goals of antihypertensive treatment are the prevention of cardiovascular events (the most frequent complication of chronic kidney disease) and the prevention or delay of greater renal impairment. Unfortunately, the evidence about the target blood pressure to be achieved in these patients is scarce and confusing [19].

Few clinical trials evaluated this specific population: the African American Study of Kidney Disease and Hypertension (AASK) study randomized patients with glomerular filtration rate between 20 and 65mL/min for aggressive treatment (target mean arterial pressure of less than 92mmHg) or usual care (target mean arterial pressure between 100-102mmHg) – there was no differences in mortality, incidence of cardiovascular events or in the progression of chronic renal disease, although aggressive treatment showed a reduction in proteinuria. Subgroup analysis, however, demonstrates that in patients with baseline proteinuria higher than 300mg/d there was a reduction in the progression of renal disease [51]. Likewise, the Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2) study showed no benefit in progression to renal disease in patients without diabetes and with nephropathy who received aggressive antihypertensive treatment (in which blood pressure ranged from 137/84mmHg to 130/80mmHg) compared with conventional treatment (in which blood pressure ranged from 136/83mmHg to 134/82mmHg) [52]. A systematic review which included 2272 patients showed that aggressive blood pressure reductions in patients with chronic renal disease did not bring significant benefits in the progression of renal disease, cardiovascular events or mortality. Thus, it seems that there are no benefits in blood pressure reductions to levels lower than 140/90mmHg and attempts at a more aggressive reduction could increase episodes of hypotension [53].

Some studies, however, suggest the presence of J-curve effect in the treatment of HTN in patients with chronic renal disease: a cohort showed that SBP levels of less than 120mmHg or DBP of less than 70mmHg have increased mortality [12]. A sub-analysis of the Irbesartan Diabetic Nephropathy Trial (IDNT) showed that blood pressure equal or less than 120/85 in patients with diabetic nephropathy caused an increase in the incidence of cardiovascular events [54].

While there is inconsistency on the presence or absence of the J-curve in HTN in patients with chronic kidney disease, the evidence supports no additional benefit in more aggressive reductions, except in patients with higher levels of proteinuria. Thus, the new guidelines suggest that drug treatment should be initiated in patients with chronic renal disease with pressure equal or higher than 140/90mmHg, with a therapeutic target of less than 140/90mmHg, although minimum safe levels are not mentioned [13, 19]. There are also recommendations for the use of ACE inhibitors or angiotensin receptor blockers in normotensive patients with diabetes only in the presence chronic renal disease (or high risk of renal disease) with albuminuria equal or greater than 30 mg/g [55].

J CURVE IN PATIENTS WITH HEART FAILURE

Hypertension is a known risk factor for heart failure, but there is little evidence from clinical trials in hypertensive patients with heart failure: most data comes from observational studies or sub-analyzes of clinical trials [56].

A review of patients enrolled in the Digitalis Investigation Group (DIG) trial, with a mean ejection fraction of 29%, showed that patients with SBP equal or less than 120mmHg have a higher incidence of hospitalization and mortality [57]. Data from a systematic review also shows that there is a mortality reduction of 13% for each 10mmHg increase in SBP [58]. We cannot, however, ignore the fact that a lower SBP can only be the result of disease progression and translate a more serious condition. Thus, despite the higher incidence of cardiovascular events in patients with heart failure and lower blood pressure levels, we cannot say that this is the result of an effect of "J-curve".

CONCLUSION

There are strong evidences that although neglected for some time, the J-curve is a current concept. There is an increase in cardiovascular events associated with more aggressive blood pressure reductions in some groups of patients: elderly, patients with CAD, patients with diabetes and possibly patients with chronic renal disease. Among patients with heart failure, the J-curve phenomenon is not clear and probably a higher incidence of cardiovascular events with lower blood pressure is associated with greater disease severity. Among patients with cerebrovascular disease or young people without co-morbidities there is no

evidence of increased cardiovascular events at lower blood pressure levels, however also there is no data on what are the minimum safe levels for treatment. Given the evidence of the J-curve in blood pressure treatment, new guidelines have suggested more permissive blood pressure levels.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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