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REVIEW ARTICLE

Hypertension, coronary heart disease and stroke: Should the blood pressure J-curve be a concern?☆

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Abstract The paradoxical increase in cardiovascular events in patients with treatment-induced low blood pressure (BP), particularly in hypertensives with pre-existing coronary artery disease, especially those with critically low diastolic BP, which conflicts with data from epidemiologic observational studies, is referred to as a J-curve. It was first described over 30 years ago and is still the subject of considerable controversy. Recent large clinical outcomes trials (INVEST, TNT, ONTARGET, PROVE IT-TIMI 22, SMART) and meta-analyses strongly support its existence for systolic and diastolic BP. The diastolic J-curve is commonly more pronounced. In contrast to cardiovascular complications related to coronary artery disease, no J-curve phenomenon was noted for stroke in most of these studies. This is explained by differences in cerebral and coronary autoregulation and because coronary perfusion occurs only during diastole. On the basis of this review, we suggest a cautious, individualized approach to treatment, particularly in hypertensive patients with coronary heart disease or high risk for impaired coronary blood flow. In these patients we advise against treatment that lowers systolic BP below 120–125 mmHg and, particularly, diastolic BP below 70–75 mmHg.

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PALAVRAS-CHAVE
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Hipertensão arterial, doença coronária e acidente vascular cerebral. A curva em J deve preocupar-nos?

Resumo O aumento paradoxal de eventos cardiovasculares quando a diminuição da pressão arterial ultrapassa determinados níveis críticos, em particular de pressão diastólica e em especial em hipertensos com doença coronária, contrariando os dados de estudos epidemiológicos observacionais, que é conhecido como curva em J e foi descrito há mais de 30 anos tendo suscitado muita controvérsia, foi novamente posto em evidência em vários estudos clínicos recentes (INVEST, TNT, ONTARGET, PROVE IT TIMI 22, SMART) e meta-análises. Na maioria destes estudos, a curva em J foi mais pronunciada para a pressão diastólica (pelo facto de a perfusão coronária se fazer durante a diástole) e não se evidenciou curva em J para acidente vascular cerebral, o que estará relacionado com diferenças nas curvas de autorregulação cerebral e coronária. Com base na análise de todos estes estudos, é nossa opinião que a atitude a tomar deverá ser prudente e individualizada, em especial em hipertensos com doença coronária comprovada ou risco acrescido para fluxo coronário comprometido (idosos, presença de hipertrofia ventricular esquerda), devendo evitar-se que se atinjam com a terapêutica anti-hipertensiva valores de pressão sistólica inferiores a 120-125 mmHg e, em particular, valores de pressão diastólica inferiores a 70-75 mmHg.

Meta-analyses of epidemiological observational studies have demonstrated a linear relationship between systolic and diastolic blood pressure (BP) levels and risk of cerebrovascular and cardiovascular events for pressures as low as 115/70 mmHg upwards. The Prospective Studies Collaboration meta-analysis of 61 studies involving a million individuals without initial cardiovascular or cerebrovascular disease showed a doubling of mortality from stroke or myocardial infarction (MI) for every 20-mmHg increase in systolic BP or 10-mmHg increase in diastolic BP.[1]

However, in a 1979 paper published in the *Lancet*, Stewart[2] suggested that there was a paradoxical increase in the incidence of MI with lower diastolic BP levels. In 169 patients with severe hypertension, those with diastolic BP (defined as disappearance of Korotkoff sounds) less than 90 mmHg with antihypertensive medication were at greater risk of MI.

In 1987, Cruickshank et al.[3] also detected a J-curve relationship between diastolic BP and mortality from MI but only in hypertensive patients with ischemic heart disease, a finding the authors attributed to the fact that coronary perfusion takes place during diastole. A subsequent meta-analysis by the same lead author of six studies involving over 14 000 hypertensive patients confirmed the J-curve relation, particularly between diastolic BP and ischemic heart disease, as well as in patients with a history of coronary heart disease (CHD).[4] The relationship between diastolic BP and coronary mortality was also seen in the Framingham study, but only in individuals with a history of MI[5]; there was no evidence of a J-curve for systolic BP. Similarly, a meta-analysis of 13 studies (48 000 hypertensives) by Farnett et al. demonstrated a J-curve relationship between diastolic BP and cardiovascular morbidity and mortality, more pronounced in the elderly and those with a history of ischemic heart disease.[6]

Although some studies have found a similar relationship with stroke,[7] most have not, and the PROGRESS trial showed that antihypertensive therapy actually reduced the risk of recurrent stroke with progressive lowering of BP.[8] Rashid et al. confirmed this finding in a subsequent review of randomized trials,[9] while Turan et al.[10] showed similar results in patients with ischemic stroke attributable to intracranial arterial stenosis, in whom the risk of stroke in the same territory was less in individuals with lower BP. A recent meta-analysis in nearly 74 000 diabetic patients showed a progressive reduction in stroke with reductions in BP, although the same was not seen for MI.[11]

However, Kannel et al.,[12] using data from the Framingham study, reported that the increased risk of cardiovascular events with diastolic BP <80 mmHg was only found when systolic BP was higher than 140 or 160 mmHg. According to these authors, the J-curve is thus related to differential (pulse) pressure, which reflects increased arterial stiffness, already identified as an important cardiovascular risk factor. In support of this hypothesis, the SHEP trial and other studies in the elderly with isolated systolic hypertension have also shown the existence of a J-curve for diastolic BP <65/70 mmHg.[13]

A meta-analysis of seven randomized clinical trials involving more than 40 000 hypertensive patients[14] showed that there is a J-curve (or U-curve) in both medicated and non-medicated hypertensives for both cardiovascular and non-cardiovascular mortality. This may be due to reverse causality, the paradoxical increase in events with lower BP levels being the consequence of poor health conditions – the result of cancer or other wasting disease, or heart failure with severely impaired systolic function.

There are thus three possible explanations for the increase in cardiovascular events with lower BP (Table 1):