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Editorial

The "hidden side of the moon" in hypertension: When and why is dangerous low diastolic blood pressure?☆

Massimo Volpe [a,b,*], Allegra Battistoni [a], Giovanna Gallo [a], Daniela Carnevale [b,c]

[a] Department of Clinical and Molecular Medicine, School of Medicine and Psychology, Sapienza University of Rome, Rome, Italy
[b] IRCCS Neuromed, Pozzilli, Italy
[c] Department of Molecular Medicine, Sapienza University of Rome, Italy

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The axiom that high blood pressure (BP) is a major risk factor for cardiovascular (CV) morbidity and mortality is widely acknowledged by the scientific community. In turn, all agree that an appropriate anti-hypertensive treatment contributes to prevent many of the long-term CV complications, but we still ignore how much challenging could be the opposite condition, i.e. when BP is too low. International guidelines now recommend a goal to maintain BP levels around 130/80 mm Hg on antihypertensive therapy [1]. European guidelines recommend BP targets not lower than 120/70 mm Hg, while US guidelines are elusive in this regard [2]. Both very low and high BP levels are linked to adverse outcomes (the "J-curve"), suggesting that aggressive intervention on BP could be counterproductive as well. However, observational studies and randomized trials (Table 1) have investigated different target thresholds. Over the years, the DBP threshold associated to risk has progressively shifted towards lower levels from 85 mm Hg [3], to 70 mm Hg [4] and now to 65 mm Hg [5]. This appears to be particularly true in patients with coronary artery disease (CAD) [6]. In fact, the study of Topel et al., in this issue of the Journal is consistent with these previous reports [7]. In a cohort of about 2000 patients with CAD, patients with DBP <60 mm Hg had the worst outcome in terms of CV death or myocardial infarction (MI) compared to patients with DBP ranging from >60 to >90 mm Hg. Patients with DBP < 60 mm Hg had higher hs-cTnI, suggesting the presence of myocardial injury. The "J-curve phenomenon" seems to be particularly relevant for coronary events and its pathophysiology is controversial. A first hypothesis was that lower DBP could be a sign of comorbidities (atherosclerosis, aortic valve insufficiency) or heart failure that could primarily influence the prognosis, increasing the rate of major CV events and deaths [8]. At present, the prevalent explanation lies on an impairment of coronary blood flow, associated to low and insufficient DBP, which approximates very closely coronary perfusion pressure that is the gradient between the coronary arteries and LV diastolic pressure [9,10]. In patients with CAD, however, coronary perfusion distal to a significant coronary obstruction, may be inadequate even in the presence of sufficient DBP, due to the additional resistance caused by the stenosis. Beside this hemodynamic hypothesis, other mechanisms cannot be excluded. In the work of Topel et al., the authors provide evidence that low DBP may trigger the activation of inflammation and immune pathways [7]. They report a different impact of low DBP on hsCRP and suPAR, being the first unaffected and the latter strongly correlated. SuPAR may be a good biomarker of vulnerable plaque [11], whereas hsCRP is more sensitive to initial inflammatory stages of atherosclerosis [12–14]. The fact that suPAR appears unrelated to hsCRP suggests that they reflect different pathophysiological stages of the inflammatory cascade triggered during the atherosclerotic process. Other observations suggest an independent role of the association between low DBP and CV risk in CAD [15–17] making hypothesize that the intensive reduction in DBP would favor a chronic state of inflammation and immune reaction.

Therefore, the J curve of coronary risk linked to very low DBP may be not the mere consequence of a hemodynamically-mediated myocardial hypoperfusion but it may involve to immune-inflammatory responses contributing to ischemia. This is a prospectively appealing area of research, which could expand our use of biomarkers and drive thereafter strategies in managing hypertension and CAD.

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* Corresponding author at: Department of Clinical and Molecular Medicine, Faculty of Medicine and Psychology, Sapienza University of Rome, Sant'Andrea Hospital, Via di Grottarossa 1035, 00189 Rome, Italy.
E-mail address: massimo.volpe@uniroma1.it (M. Volpe).

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Table 1
J curve in hypertensive with coronary artery disease according to diastolic blood pressure levels.

Reference	Sample size and subjects included in the study	J-curve point (mm Hg)	Events associated in J-shaped mode with BP and other findings
Framingham study [18]	5209 patients, 30–62 years old, with or without previous MI	DBP: 75–79 mm Hg	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 [19]	3080 high-risk hypertensive patients	DBP: 80 mm Hg	J-shaped relationship was found only between DBP and myocardial infarction.
INVEST [20]	22,576 hypertensive patients with coronary artery disease ≥ 50 years old	SBP/DBP: 129/74 mm Hg	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 [21]	7665 patients with concurrent stable angina and hypertension	–	J curve was found between DBP and cardiovascular events, but no among DBP and stroke.
TNT [22]	10,001 patients 35–75 years old with coronary artery disease and LDL < 3.36 mmol/l	SBP/DBP: 146.3/81.4 mm Hg	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 [23]	4162 patients with acute coronary syndrome	SBP/DBP: 110/70 mm Hg	J-shaped relationship was found between SBP and DBP and all-cause mortality, myocardial infarction, unstable angina, revascularization after 30 days and stroke.
Syst-Eur 2009 [24]	4695 > 60 years, isolated systolic hypertension	DBP: <70 mm Hg	J-curve only in patients with coronary heart disease at baseline
SHEP 1999 [25]	4736 > 60 years, isolated systolic hypertension	DBP: 70 mm Hg	increased risk for cardiovascular events with DBP < 70 mm Hg was observed in the treated group of patients
McEvoy et al. [15]	11,565 adults	DBP 60–69/<60 mm Hg	J curve for Progressive myocardial damage (hsTnI) incident CHD and mortality, but not for stroke. Especially when SBP > 120 mm Hg

SBP: systolic blood pressure, DBP: diastolic blood pressure, CHD: coronary heart disease; TnI: troponin I; MI: myocardial infarction; ACTION: A Coronary disease Trial Investigating outcome with Nifedipine, HOT: the Hypertension Optimal Treatment, INVEST: the International Verapamil-Trandolapril Study, PROVE – IT TIMI: PRavastatin Or atorVastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction study, TNT: Treating to New Targets study.

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