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Blood pressure cut-offs to diagnose impending hypertensive emergency depend on previous hypertension-mediated organ damage and comorbid conditions

GORAN KORACEVIC, MILOVAN STOJANOVIC, DRAGAN LOVIC, TOMISLAV KOSTIC, MILOJE TOMASEVIC, SONJA SALINGER MARTINOVIC, SNEZANA CIRIC ZDRAVKOVIC, MAJA KORACEVIC, VLADIMIR STOJANOVIC

ABSTRACT

Background. Hypertensive emergencies (HTN-E) are important due to a high risk of mortality. However, a sudden increase in blood pressure (BP) can damage target organs before the BP reaches cut-offs to diagnose HTN-E. We (i) analyse HTN guidelines for recommendations of treatment individualization, such as adjusting BP cut-offs for hypertensive urgency or impending HTN-E according to patient's susceptibility to complications (because of previous hypertension-mediated organ damage [HMOD], cardiovascular events and comorbid conditions), and (ii) provide a rationale for the inclusion of patient's susceptibility in protocols for treatment of acute HTN-E.

Methods. We searched PubMed, SCOPUS, Science Direct, Springer, Oxford Press, Wiley, SAGE and Google Scholar for the following terms: arterial hypertension, impending, emergency, target organ damage, hypertension-mediated organ damage, and comorbidity.

Results. The available guidelines do not recommend that when we estimate the probability of HTN-E in a patient with very high BP, we take into account not only the 'aggressive factor' (i.e. history of HTN, absolute BP values and rate of its increase), but also the 'vulnerability of the patient' due to previous major adverse cardio-vascular events, HMOD and comorbid conditions.

Conclusion. The risk does not depend only on the aggressiveness of the health threat but also on the strength of the host's defence. It is, therefore, surprising that one side of the natural interaction (i.e. susceptibility of a patient) is overlooked in almost all available guidelines on HTN.

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University Clinical Center Nis, Serbia
GORAN KORACEVIC, TOMISLAV KOSTIC, SONJA SALINGER MARTINOVIC, SNEZANA CIRIC ZDRAVKOVIC, VLADIMIR STOJANOVIC Department for Cardiovascular Diseases

Institute for Treatment and Rehabilitation Niska Banja, Nis, Serbia
MILOVAN STOAJNOVIC

Clinic for Internal Diseases Inter Medica, Nis, Serbia
DRAGAN LOVIC

University of Kragujevac and University Clinical Center of Serbia, Belgrade, Serbia
MILOJE TOMASEVIC Faculty of Medicine and Department for Cardiovascular Diseases

Serbia Innovation Center, University of Nis, Serbia
MAJA KORACEVIC

Correspondence to MILOVAN STOJANOVIC;
milovanstojanovic1987@gmail.com

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INTRODUCTION

Hypertensive emergencies (HTN-E) are important due to the high prevalence and high mortality risk. Caligiuri *et al*.[1] found that nearly 2% of the population had an asymptomatic HTN-E/hypertensive urgency (HTN-U). It has been reported that 1% to 2% of patients with hypertension (HTN) will have a HTN-E during their life-time.[2] It has been shown 25 years ago that over one-fourth of patients admitted to the emergency department have HTN-E or HTN-U;[3] this is far more than the recent finding of about 2%.[4]

There is also an increased risk of mortality. Almost a century ago (in 1928), the 1-year mortality was 80% and it decreased to 10% 70 years later.[2] Nowadays, mortality at 90 days is about 4% for HTN-U and 16% for HTN-E.[5]

The individualization is a good principle in medicine.[6] Not all patients are equal also in the field of HTN. In patients without chronic HTN, HTN-E can occur at considerably lower blood pressure (BP) values (e.g. pregnant women with pre/-eclampsia).[7]

The aim of the review is twofold: to analyse HTN guidelines for recommendations of treatment individualization, such as adjusting BP cut-offs for HTN-U or impending HTN-E according to patient susceptibility to complications (because of previous hypertension-mediated organ damage [HMOD], cardiovascular events and comorbid conditions); and to give rationale for the inclusion of patient susceptibility in protocols for treatment of acute HTN-E.

METHODS

We searched PubMed, SCOPUS, Science Direct, Springer, Oxford Press, Wiley, SAGE and Google Scholar. All retrieved abstracts were analysed about the relevance considering HTN-E and HTN-U. If the abstract was relevant, the papers were retrieved and studied in detail. There were no limits regarding time and language to evaluate the abstracts. Full-length papers in English language were used.

We searched for the following terms and also for a variety of their combinations: 'arterial hypertension', '*impending*',

'emergency', 'target organ damage', 'hypertension-mediated organ damage' and 'comorbidity'. We performed a narrative review because there are no randomized clinical trials available on the topic.

LITERATURE OVERVIEW

A sudden increase in BP can damage target organs before it reaches cut-offs to diagnose HTN-E.[8] The BP levels sufficient for HTN-E to occur are markedly different in individual patients. On the one hand, patients with long-standing HTN have more pronounced hypertrophy of the smooth muscle (aiming to decrease wall stress) and are capable of sustaining higher BP levels without HMOD. On the other hand, HTN-E can occur at substantially lower levels of BP in previously normotensive patients or in the ones with recent-onset HTN; among other reasons, smooth muscle hypertrophy is generally absent (and consequent capillary protection).

HTN-Us are frequently seen in the emergency department, usually after stress, excess of food (particularly salty), alcohol or effort, or following omission of antihypertensive drug(s). HTN-U is an excellent example of the importance of the patients' previous health condition, e.g. usual BP in individuals with an average BP of 85/60 mmHg before the event, BP not higher than 140/90 (due to high relative increase of mean BP) may lead to symptoms of HTN-U such as severe headache, vomiting and instability. Importantly, the diagnosis of HTN-U is one of exclusion: if there are suggestive symptoms, we need to prove that there is not an acute HMOD associated with very high BP. It usually requires laboratory (e.g. cardiac troponin to exclude myocardial lesion), ECG (to exclude myocardial ischaemia), CT scan of the head (to exclude neurological HTN-Es, e.g. stroke), etc. This approach is recommended in most guidelines. In contrast, the European Society of Cardiology (ESC) Council suggests avoiding the term HTN-U as such patients have a prognosis similar to patients with severe HTN.[9]

Generally, it is accepted that the severity of the HTN crisis depends on the actual as well as previous BP and on the rate of increase in BP.[2,9,10] Patients with very high BP present with HTN-E or HTN-U. This is the result of two factors: (i) the previous state (patients' general health, including cardiovascular and other diseases, and his/her HTN-related conditions, including the duration and severity of HTN, usual BP values, the number and the severity of HMOD, etc.); and (ii) the rate, the magnitude and the cause of increase in BP. The second factor is clearly recognized by many guidelines on the topic[2,9,10] but the first is missed by most (Fig. 1).

Therefore, in addition to diversity among HTN-E types (e.g. aortic dissection [AoD], eclampsia, acute myocardial infarction [MI]), there are obvious differences among both HTN-E and HTN-U patients regarding duration and severity of HTN, as well as rate of BP increase, triggers, etc.; previous HMOD, and the number of comorbid conditions, their kind (diabetes mellitus, renal failure, etc.), and severity.

In such a scenario, is there a consequent individualization regarding BP cut-offs for the diagnosis of HTN-U and HTN-E? The present literature suggest that it is not so except the indirect suggestion of relativity in the phrase 'BP *usually* above…'.[11,12] While precise guidance for each type of patient is not possible, there is not even a general suggestion with some suggestions or recommendations. Further, there is a substantial variability in the characteristics of patients with HTN. Therefore, no physician believes that any BP value is an optimal cut-off (to diagnose HTN crisis) for the whole population with HTN. In line with this, against 'one-size-fits-all' principle, numerous guidelines suggest that definitions of HTN-U or HTN-E require systolic BP values *usually* >180 mmHg. Moreover, underlining the rate of BP changes, the majority of guidelines support the individualization, by taking previous BP readings into account.

Indeed, when deciding the treatment the most important factor is the *degree of patient's risk.* This is also true for HTN-Us and HTN-Es; the higher the risk with very high BP, the more effective the reduction in BP ought to be. *The crucial point is that the risk does not depend only on one side, on the aggressiveness of the health threat, but also on the strength of the host's defence*. In general, any result of interaction between the two opposed factors depends on both factors; this is logical and recognized in many areas in medicine. It is therefore surprising that one side of the natural interaction (i.e. susceptibility of a patient) is overlooked in almost all available guidelines on HTN (the documents guiding our practice in the field of HTN; Table I). When citing various guidelines from the same society or association, it is usual to choose the most recent one, as it is an updated, improved version. The exception is when a certain edition of the guideline does not relate to the topic. In this instance, we used the Seventh Joint National Committee (JNC7) instead of JNC8, as JNC8 does not elaborate on HTN-E, HTN-U or HTN crises.

There is a striking analogy in the pathophysiology of numerous cardic diseases with an imbalance between the aggressive factor and host defence (Table II).

There is an important (unnoticed until recently) problem regarding HTN-U and HTN-E; the very high BP and severe

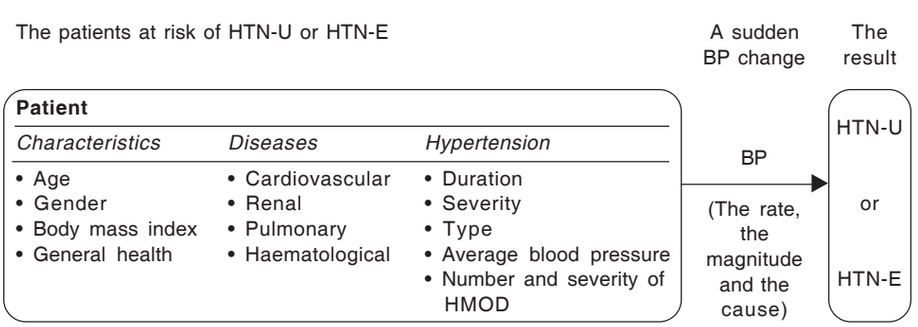

FIG 1. The patients' vulnerability to the genesis and outcomes of hypertensive crisis
HTN arterial hypertension HMOD hypertension-mediated organ damage
BP blood pressure HTN-U hypertensive urgency HTN-E hypertensive emergency

TABLE I. Recommendations by different guidelines of treatment individualization (such as adjusting blood pressure cut-offs for hypertensive emergencies or hypertensive urgency) and patient's susceptibility to complications partially due to previous hypertension-mediated organ damages(s) and cardiovascular events and comorbid conditions

Guideline	BP cut-off for HTN-E (mmHg)	BP cut-off for HTN-U (mmHg)	Adjusting BP cut-offs (for HTN-E or HTN-U) to the individual characteristics	Patient susceptibility to complications due to previous HMOD(s), cardiovascular events and comorbid conditions when determining BP cut-offs and treatment
Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High BP[13]	>180/120	Upper levels of stage II HTN	–	–
Dutch guideline for the management of hypertensive crisis, 2010 revision[7]	Diastolic >120–130; systolic >200–220	Diastolic >120–130; and sBP >200–220	–	–
2013 ESH/ESC guidelines for the management of arterial hypertension[14]	sBP>180 dBP>120	'Large BP elevation'	–	–
South African hypertension practice guideline, 2014[17]	Severe hypertension (stage 3 dBP≥110 and/or sBP≥180)	Severe hypertension (stage 3 dBP≥110 and/or sBP≥180)	–	–
2017 ACC/AHA/AAPA/ABC/ACPM/ AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High BP in Adults[18]	sBP>180 dBP>120	sBP>180 dBP>120	–	–
Kenya National Guidelines for Cardiovascular Diseases Management, 2018[19]	>180 or >120	Severe elevations in BP	–	–
Management of Hypertension in the SESLHD Ward Settings, 2018[20]	sBP>180 dBP>120	sBP>180 dBP>120	–	–
2018 Chinese Guidelines for Prevention and Treatment of Hypertension[21]	Severely increases (generally over 180/120)	Severe elevated BP level	–	–
Academy of Medicine of Malaysia. The CPGs; Management of Hypertension (5th edition), 2018[22]	≥180/110	≥180/110	'HTN-Es may occur in patients with BP <180/110 mmHg, particularly if the BP has risen rapidly'	–
2018 ESC/ESH Guidelines for the Management of Arterial Hypertension[10]	Severe HTN (usually grade 3)	Severe HTN	–	–
Hypertension Canada's 2018 guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of Hypertension in Adults and Children[23]	Severe elevation of BP	Severe elevation of BP	–	–
The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2019)[24]	Sustained marked HTN (usually ≥180/120)	Sustained marked HTN (usually ≥180/120)	'In patients with hypertensive encephalopathy related to a rapid increase in BP, eclampsia or AoD, emergency treatment is often necessary even when BP is not abnormally high'	'However, treatment by hospitalization is also necessary for a hypertensive urgency in high-risk patients such as those with a history of cardiovascular diseases'
ESC council on hypertension position document on the management of hypertensive emergencies[9]	Very high BP values (often >200/120)	–	–	–
Brazilian position statement on hypertensive emergencies, 2020[25]	sBP ≥180 dBP ≥120	sBP ≥180 dBP ≥120	–	–

HTN arterial hypertension HTN-E hypertensive emergency HTN-U hypertensive urgency HMOD hypertension-mediated organ damage BP blood pressure sBP systolic BP dBP diastolic BP ESH European Society of Hypertension ESC European Society of Cardiology CPG Clinical Practice Guideline AoD aortic dissection ACC American College of Cardiology AHA American Heart Association AAPA American Academy of Physician Assistants APhA American Pharmacists Association NMA National Medical Association PCNA Preventive Cardiovascular Nurses Association JNC8 Eighth Joint National Committee ABC Association of Black Cardiologists ACPM American College of Preventive Medicine AGS American Geriatrics Society ASH American Society of Hypertension ASPC American Society of Preventive Cardiology SESLHD South Eastern Sydney Local Health District

TABLE II. Diseases and clinical conditions in which 'the strength of an aggressive factor' and 'the vulnerability of the patient' should be taken into account

Study reference number	Disease/clinical condition	Type/consequence of disease ('threat' for the patient's health)	Contrary type/consequence of disease ('weakness/susceptibility' of the patient)	Practical implication
26	Acute myocardial infarction, dual antiplatelet therapy	Coronary artery rethrombosis	Bleeding	Bleeding risk should be evaluated too
27	Atrial fibrillation, oral anticoagulant therapy	Thromboembolism (CHA_2DS_2VASC score to predict it)	Bleeding (HAS-BLED score to predict it)	'Net clinical benefit' should be analysed (thromboembolic *v.* bleeding risk)
28	Aortic dissection, aortic aneurysm	Hypertension	Weakness of the aortic wall, e.g. Marfan syndrome, glucocorticoid use	Both factors should be analysed (and controlled, if possible)

complaints impose a need for antihypertensive treatment, either intravenous (in case of HTN-E) or peroral (if the diagnosis is HTN-U). Which one to administer (parenteral or peroral drug) is frequently not straightforward, until the acute HMOD is confirmed or denied. Some of the investigations (e.g. computed tomography) are time-consuming and during this period a mistake is possible: to treat HTN-U as if it is HTN-E or the other way round.[29] As we noticed, one of the problems regarding HTN-E and HTN-U is that their differentiation often cannot be done at once (within several minutes). The delay results not only due to patient-related reasons, but also due to medical service functioning. Even with the optimal symptom-to-physician time flow, additional time is often necessary, e.g. imaging methods to be organized, performed and interpreted. During this period, it is frequently not possible to be sure that the drug administration (parenteral or peroral) is adequate for the particular patient.

Therefore, there is a knowledge gap in how to treat patients with very high BP until we perform laboratory and imaging analyses to distinguish between HTN-U and HTN-E.[29]

Importance of HMOD, previous cardiovascular events and comorbid conditions

According to the latest international HTN guideline, HMOD includes lesions of the heart (such as left ventricular hypertrophy [LVH]), brain, kidneys, eyes as well as central and peripheral arteries. Common comorbid conditions and complications include coronary artery disease (CAD), stroke, chronic kidney disease, heart failure (HF) and chronic obstructive pulmonary disease.[30]

There is a consensus for decades that HTN-E represents an association between very high BP and an acute HMOD. It is presented as a 'Result' in the simplified scheme in Fig. 1. This definition is valid regardless of the presence of pre-existing HMOD.

Our observation is that this definition of HTN-E and correct characterization of the rate and extent of BP elevation presented as 'BP increase' in Fig. 1 are not complete in terms of missing the starting point, i.e. patient's vulnerability to HTN-E or HTN-U. It is likely both from the known principles and from clinical experience that 'the starting point' matters, for example, the likelihood of sBP reaching 180 mmHg (the usual cut-off for BP associated with HTN-U or HTN-E) is much higher if a patient has an average sBP of 160 mmHg compared to sBP of 125 mmHg. Moreover, the likelihood of an acute HMOD is generally higher in the organ that is already damaged (when there is a certain degree of a chronic HMOD). Hence, the rate of complications depends not only on BP level, but also on HMOD, previous cardiovascular events and comorbid conditions. For example, the probability of an acute HF depends not only on how high BP is but also on the previous HF, MI, left ventricular ejection fraction (LVEF), etc. A smaller increase in BP (compared to individuals without HF) is generally needed to cause 'afterload mismatch' and results in decompensation in patients with reduced LVEF (HF with reduced ejection fraction [EF]),[31] as well as in HF with preserved LVEF (HF with preserved EF).[32] Consequently, the BP threshold for complication—acute cardiogenic pulmonary oedema—is lower in comparison with patients without HF.[32] Therefore, if the BP cut-off for HTN-E is generally 180 mmHg for sBP according to recent guidelines[10,13,14,16–22,24,25] for a patient with poor left ventricle, the cut-off should be lower (e.g. sBP 160 mmHg). Hence, the BP level needed for acute pulmonary oedema (which is HTN-E) is not equal for all patients, since it depends on the HMOD (left ventricular hypertrophy) and previous cardiovascular events (such as MI). In stable HF (in remission), substantial increase in BP is one, but an important, risk factor of the numerous risk factors for worsening of the clinical course.[33–35]

Similar or even lower BP cut-offs should be considered for patients with diagnosed aneurysm of the aorta, carotid artery, coronary artery, etc. In papers on acute aortic dissection, both types of risk factors are listed: (i) an aggressive factor, e.g. HTN and (ii) a weak aortic wall (diseases which make aorta susceptible to dissection/rupture such as Marfan syndrome, Ehler–Danlos syndrome, etc.). These two types of risk factors are not mentioned/explained sufficiently in the numerous papers on HTN. Therefore, the focus only on high BP level (disregarding the capacity of the patient to resist it) is conceptually insufficient. The essential thing is to add factors that decrease the threshold for certain HTN-E into account when considering an individual risk for this HTN-E.

In addition to HMOD and previous cardiovascular events, estimated risk also depends on comorbid conditions. For example, acute pulmonary oedema is more likely with the same cardiac status if a patient has low albumin level or renal failure or if there is just a severe fluid overload (from, e.g. iatrogenic reasons such as too many infusions). Moreover, some of comorbid conditions, e.g. anaemia, renal failure and hepatic failure increase the risk of bleeding (including intracranial) in patients with very high BP. Therefore, comorbid conditions have an evident effect on the

patients' risk of HTN-E. This is in line with recognized predictors for HTN-Es, including anaemia ($p<0.0001$), history of CAD ($p<0.001$), congestive HF ($p<0.001$) and chronic renal insufficiency ($p<0.001$).[36] Therefore, the BP cut-offs for HTN-E should be lower in the presence of previous organ damage and comorbid conditions.

DISCUSSION

Impending HMOD is a long-standing concept, used for decades in many papers.[37,38] However, it is intrinsically difficult to define the term 'impending HMOD', because of inadequate methodology to predict who, when and at which BP level will experience an acute HMOD.[39] Recently, the definition of an impending HMOD has been suggested as sufficiently high BP (in a patient with plausible clinical picture) to be probably associated with an acute HMOD, for example, sudden elevation of BP to a high level of 230/130 mmHg in a patient with worsening ('crescendo') angina pectoris for several days.[39]

The 'impending HMOD' is an important, long-standing concept used in the definitions of HTN-E and allowing prompt but careful intravenous antihypertensive drug usage before the acute HMOD occurs (aiming to prevent it). Previous and current guidelines have focused on the fact that not all high BPs impose an equal risk; the large difference in risk exists between HTN-E and HTN-U, despite often similar BP levels. It is frequently overlooked that not all patients are equal. Considering high BP as an indication for treatment, we usually think of individuality in the light of previous BP values: for a young woman with a usual BP of 90/60 mmHg, an increase to 140/90 can be unpleasant. Moreover, 160/100 mmHg with symptom(s) (e.g. headache) can be regarded as HTN-U. Furthermore, this risk stemming from patient's susceptibility to HTN-E is also not elaborated in the guidelines.

Conclusion

Events that result from the relation of two opposite entities depend on both of them; the imbalance can result either from a strong aggressive factor or by insufficient defence (or by a combination of the two). When the defence is jeopardized, a lower level of aggression is sufficient to cause harm.

It is not recommended in available guidelines that when we estimate the probability of HTN-E in a patient with high BP, we ought to take into account not only 'aggressive factor' (i.e. history of HTN, absolute BP values and rate of its increase), but also the 'vulnerability of the patient' due to previous major adverse cardiovascular events, HMOD and comorbid conditions.

In all HTN guidelines with a description of HTN crises and their treatment, there is a definition of HTN-E as a high BP with the acute HMOD. In some guidelines, it is stated that the rate and the extent of BP increase also matters. What is rarely (if ever) mentioned is that the likelihood of HTN-Us and HTN-Es depend also on the patients' vulnerability (susceptibility to HTN crises). The increase in BP resulting in HTN-U or HTN-E resembles strikingly any movement/travel; the condition at the destination does not depend solely on the speed and the travelling distance, but on the condition at the start, too.

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