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Review
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The gray zone in severe hypertension – from uncontrolled to hypertensive emergencies: where one stops and the other begins

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Abstract

Acutely increased blood pressure (BP) is a very common presentation in the emergency department (ED). However, not every high BP value represents a life-threatening condition; therefore, adjusting antihypertensive treatment and focusing on long-term BP control is often sufficient. Nonetheless, acute severe increase in BP associated with acute hypertensive-mediated organ damage (HMOD), the real hypertensive emergencies (HEs), require quick diagnosis and adequate therapy to prevent or diminish acute organ dysfunction. Easy in theory but hard in practice, a clear distinction between uncontrolled hypertension (UH) and HEs is not always readily apparent until evidence of organ damage appears, leaving the clinician in a "gray zone" of BP values and time of unknown approach to the intensity and rapidity of lowering BP and subsequent cardiovascular risk control. UH is the most frequent form of ED presentation for an acute increase in BP. In these patients, it is reasonable to lower BP with caution and within a few hours without aiming to get a BP within the normal range. The true aim is, however, to obtain long-term control of hypertension and risk factors. On the other hand, HE requires a supervised, tailored approach according to the acute HMOD. A customized timeline and magnitude of BP decrease is mandatory and the patients should be admitted for monitoring. Therefore, the cornerstone in the management of acute hypertensive disorders remains the accurate definition and risk stratification of the actual emergency and a tailored therapeutic strategy.

Keywords: hypertensive emergency, uncontrolled hypertension, cardiovascular risk, acute hypertension mediated organ damage, blood pressure control.

Introduction

Modern management of very high blood pressure (BP), defined as BP ≥180/120 mmHg, should start from a clear separation between two entities: uncontrolled hypertension (UH) and hypertensive

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emergency (HE). However, BP value itself cannot distinguish one condition from another.

Most patients with elevated BP have no acute, end-organ injury, and they are by definition a part of the UH group. If aggressive therapy is started, there may be more risks than benefits in this group, so it is essential to rule out a real emergency before beginning a specific antihypertensive regimen. Symptoms such as anxiety, headaches, palpitations, epistaxis, or even mild dyspnea may be present [1].

In contrast, hypertensive emergencies (HEs) are uncommon, accounting for less than 1 percent of all visits to the emergency department (ED) [2], and can develop in patients with or without known preexisting hypertension. Patients who have signs and symptoms of acute organ damage are those considered HEs, and immediate BP control should be initiated (minutes, hours).

BP levels alone do not reliably predict the presence of acute hypertension mediated organ damage (aHMOD) and should be suspected according to the presenting signs and symptoms [3]. The differences in cardiovascular risk factors and prognosis between UH and HEs are poorly investigated [3].

A clear distinction between UH and HEs remains a challenge in the ED. Therefore, we conducted a descriptive review to gather the most recent studies regarding the accurate diagnosis of HEs and their negative predictive factors in an effort to improve the recognition and risk stratification in patients referred to the ED.

Diagnosis of hypertensive emergencies

HEs are those situations where very high BP values are associated with acute organ damage; hence, immediate BP reduction and control is a priority [4].

Acute end-organ damage caused by hypertension can manifest in one or several organ systems. The most frequent manifestations are acute neurological signs and symptoms (stroke, hypertensive encephalopathy), acute pulmonary edema and/or cardiac ischemia, followed by aortic dissection, and malignant hypertension with or without acute kidney injury (AKI) [3]. Symptoms considered suspicious of aHMOD are: chest pain (89.0%), visual disturbances (89.8%), dyspnoea (82.7%), headache (82.1%), dizziness (52.0%), conjunctival haemorrhages (41.5%), tinnitus (38.2%) and epistaxis (34.4%) [5].

There is no specific BP threshold to define HE. Every presentation in the ED for an acute rise in BP should be managed carefully. A meta-analyze conducted by Astartitaa *et al.*, who studied the prevalence of hypertensive emergencies and urgencies at the ED, showed that BP levels alone do not reliably predict the presence of aHMOD [3]. Hence, establishing the presence or absence of aHMOD must be the key step in the diagnostic process.

A review of the clinical picture timeline and the patient's medical history can help identify possible triggers for the severe BP increase. Common findings are non-adherence to treatment and lifestyle, recent discontinuation of antihypertensive drugs known for their rebound effects, use of certain drugs (non-steroidal anti-inflammatory drugs (NSAIDs), steroids, cyclosporine, sympathomimetics, cocaine, anti-angiogenic therapy) or the presence of secondary hypertension (kidney disease or renal artery stenosis) [4].

A hierarchical, symptom-based strategy was proposed by Van den Borg *et al.* to diagnose HEs accurately. This strategy takes into account five main symptoms as entry criteria: chest pain, acute dyspnea, neurological symptoms, headache, and visual impairment. A recent study has shown that this strategy can exclude HEs with a 99% negative predictive value in the absence of all the five symptoms. However, in the same population, the positive predictive value of the symptom-based strategy was low (23%), underpinning the need for a more comprehensive evaluation and risk stratification to guide acute clinical management in the ED [6].

A systematic approach should be used to define the type of HE. Clinical findings and medical history are the basis from which specific investigations will be requested. This further work-up is necessary to establish whether there is aHMOD present and initiate appropriate treatment according to the organ affected (Table 1).

Though it is easier to group HEs by the target organ involved, acute multiple organ damage must be taken into account [7].

Specific investigations

F. Saladini *et al.* designed a questionnaire for specialists in some areas of Italy regarding diagnosis strategies in HEs and UH. The most common tests prescribed to assess organ damage were electrocardiography (ECG) (97.2%), serum creatinine (91.4%), markers of cardiomyocyte necrosis (66.2%), transthoracic echocardiography (TTE) (65.1%), brain-computer tomography (CT scan) (57.1%), urinalysis (54.8%), chest radiography (50.7%). Specialists considered fundoscopy a necessary investigation in less than 50% of cases and prescribed it less often (27.2%) mainly because this investigation was not available in the rest of 21.7% of cases [5]. The ESC Council position statement on HEs recommends fundoscopy as a first-line examination in patients that present at the ED with increased BP, especially if malignant hypertension is suspected.

Table 1. Assesment of acute, hypertension-mediated organ damage (HMOD). Usual laboratory tests*: Haemoglobin, Platelet count, Fibrinogen, Serum creatinne, electrolytes, LDH – lactate dehydrogenase, Haptoglobine, Quantitative Urinalysis (proteins, erythrocytes, leucocytes, cylinders, casts), Troponin, CK, CK-MB. CT – Computer tomography; ECG – electrocardiography; HELLP syndrome – Hemolysis, Elevated Liver enzymes, Low Platelet count.

Acute HMOD	Specific clinical findings	Recommended investigations
Brain • Hypertensive encephalopathy • Acute ischaemic/haemorrhagic stroke • Posterior reversible leukoencephalopathy syndrome	Acute head injury/trauma; Nausea; Vomiting; Focal neurologic symptoms; Generalized neurologic symptoms – seizures, visual disturbances, delirium, agitation.	• **Magnetic resonance** – T2/flair = confirm diagnosis • **CT scan** – to exclude intracerebral haemorrhage • **Laboratory tests***
Retina • Papilloedema hemorrhages • Retinal edema	Reduced vision; Visual disturbances; Headache; Eye swelling.	• **Fundoscopy** **Grade III:** flame shaped haemorrhages, cotton wool spots **Grade IV:** papilloedema **Laboratory tests***
Heart • Acute coronary syndrome • Acute cardiogenic pulmonary oedema • Acute heart failure	Chest discomfort or pain; Dyspnea; Peripheral edema.	• **ECG**; • **Chest X-ray** – fluid overload • **Lung ultrasound** – B lines • **Echocardiography** • **Laboratory tests***
Kidney • Acute kidney failure	Decreased urine output; Fluid retention.	• **Renal ultrasound** Kidney size, obstruction • **CT – Abdominal** • **Laboratory tests***
Vessels • Acute aortic dissection • Microangiopathic hemolytic anemia	Chest pain; Severe back pain.	• **Echocardiography + aorta** • **CT – angiography** thorax and abdomen • **Laboratory tests***
Uterus • Eclampsia • Severe pre-eclampsia • HELLP syndrome	Headache; Vision problems; Nausea & Vomiting; Swelling.	• **Fundoscopy** • **ECG** • **Laboratory tests*** • **Imaging according to signs and symptoms Assessment of foetal wellbeing**

A grade III or IV hypertensive retinopathy is a marker of disrupted cerebral autoregulation, and a rapid BP decrease in these cases could lead to cerebral hypoperfusion [8]. Whether fundoscopy should play a significant role at least in the management decisions of HEs and UH, for instance, the degree and rapidity of BP lowering, is still under debate. However, data suggest that in patients with advanced retinopathy, an inpatient, supervised, progressive BP reduction is advisable in order to prevent cerebral ischemia [9].

Gray zone – Defining risk factors for hypertensive emergencies

Age, sex, and ethnicity are the three pillars of cardiovascular risk factors on which many others cumulate and weaken the entire structure.

A particular hypertensive population is represented by the old, frail patients prone to have rapid evolution towards end-organ damage when presenting with high BP values. Their increased risk for developing aHMOD requires particular attention [10, 11]. Chronic heart failure (HF), chronic kidney disease (CKD), coronary artery disease (CAD), and history of stroke are the most common comorbidities found in a large frail proportion of patients presented in ED [12, 13]. The absence of a documented and detailed medical history for those preexisting conditions may lead to misdiagnosis and mistreatment.

Elderly patients are highly susceptible to having an episode of HE, as suggested in a single-center report, especially in those known with hypertension and other comorbidities (atrial fibrillation, chronic coronary syndromes, history of stroke, dyslipidemia) [12].

In a recent systematic review of hypertensive crisis risk factors, Benenson *et al.* found that the risk

was higher in patients with a history of CKD (odds ratio [OR] 2.899, 95% confidence interval [CI] 1.32, 6.364), coronary artery disease (OR 1.654, 95% CI 1.232, 2.222), or stroke (OR 1.769, 95% CI 1.218, 2.571) [13]. Though patients with HEs had a higher mean systolic BP, the difference was small and not clinically significant.

Men seem to be more prone to develop a HEs and have a higher adjusted 3-year all-cause mortality compared with women [13] (hazard ratio [HR], 1.14; 95% confidence interval [CI], 1.01-1.29; p=0.031), especially among patients over 50 years old (HR, 1.14; 95% CI, 1.01-1.29; p=0.038). Moreover, hospitalizations for HEs and UH have steadily increased in the past years, slightly more among men than women [14].

African American patients have a higher prevalence of severe hypertension and an increased incidence of malignant hypertension and related renal failure [15]. However, it is unclear if there is a racial-associated increased risk for progression to HE apart from the high prevalence of severe hypertension in this patient population [16].

Patients with a history of ED presentations for poor BP control are more likely to have recurrent UH episodes and an increased risk for HEs if BP and risk factors remain uncontrolled. Compliance with treatment continues to be a challenging issue to manage in many low and middle-income countries [16–18].

Management overview

Type of aHMOD drives treatment in patients with HEs. Except for patients with acute ischaemic/hemorrhagic stroke, there are no randomized controlled trials (RCT) for the rest of HEs, so their management is mainly based on clinical experience, observations, and comparisons on intermediate outcomes [4, 19].

In patients with UH, simple actions such as placing the patient in a comfortable and quiet room for 30 minutes can significantly reduce BP in 1 out of 3 hypertensive patients [20]. Grassi *et al.* showed that 31.8% of 549 patients with UH had a spontaneous reduction of more than 20 mmHg systolic BP and 10 mmHg diastolic BP within 30 minutes of quiet rest [21].

In general, it is not advised to lower BP too rapidly or too low as vascular beds that are chronically exposed to high pressures can suffer from relative ischemic damage [2]. In chronic hypertensive patients with poor BP control, the autoregulatory curve is entirely right-shifted; hence, reducing BP down to 20–25% from the maximum value should be the threshold [1]. In most cases, mean arterial pressure (MAP) should be reduced by 10–20% in the first hour and by a further 5–15% over the next 23 hours [22]. In order to achieve a controlled and timely decrease in BP, intravenous antihypertensive drugs should be used.

Neurologic emergencies are the most challenging. Their clinical manifestations can be very similar, and the differential diagnosis is essential given the fact that they have different treatment strategies. For instance, in patients with acute ischemic stroke, the reduction of BP must be strictly controlled, and antihypertensive therapy should be administered only when BP exceeds 220/120 mmHg, in patients who are not candidates for thrombolytic therapy and only if it exceeds 185/110 mmHg in patients who undergo thrombolysis. In contrast, in patients with hemorrhagic stroke, the systolic BP goal should be between 130–180 mmHg (Figure 1), requiring treatment if BP>185/110 mmHg. The drugs of choice should be Labetalol, Nicardipine, or Nitroprusside.

However, there are situations where a rapid and abrupt decrease in BP is mandatory. Acute aortic dissection has an opposite approach requiring an urgent reduction of systolic BP to 100–120 mmHg and heart rate <60 bpm in less than 30 minutes. The drugs of choice include Esmolol/Labetalol and Nitroprusside, Nitroglycerine, or Nicardipine [23].

Prognosis – can it be improved?

Uncontrolled hypertension

The term hypertensive "urgency" has gained more and more attention in recent years because it underlies a misperception of what it really means. It ends up conferring an undue sense of gravity to a non-urgent condition. It encourages providers to treat these patients with a rapid reduction in BP despite the fact there is no evidence to support this approach [24]. The newest recommendations include using uncontrolled hypertension (UH) instead of hypertensive urgency [4]. Severe BP elevation with no symptoms is a frequent discovery in the office setting. Recent evidence suggests that immediate referral to ED is neither necessary nor associated with improved outcomes [25, 26].

A retrospective cohort study conducted by Patel *et al.*, which included 58,535 patients with UH, showed no difference in major adverse cardiovascular events (MACE) at 7 days, 1 month or 6 months (overall MACE <1%) between ambulatory and inpatient management. Visits to the ED were associated with more hospitalizations but not with improved outcomes. Furthermore, most patients still had UH 6 months later [26].

UH is a more likely cause of long-term cardiovascular morbidity and mortality; hence, intensification of antihypertensive treatment should be emphasized [27] and is more important than urgent BP

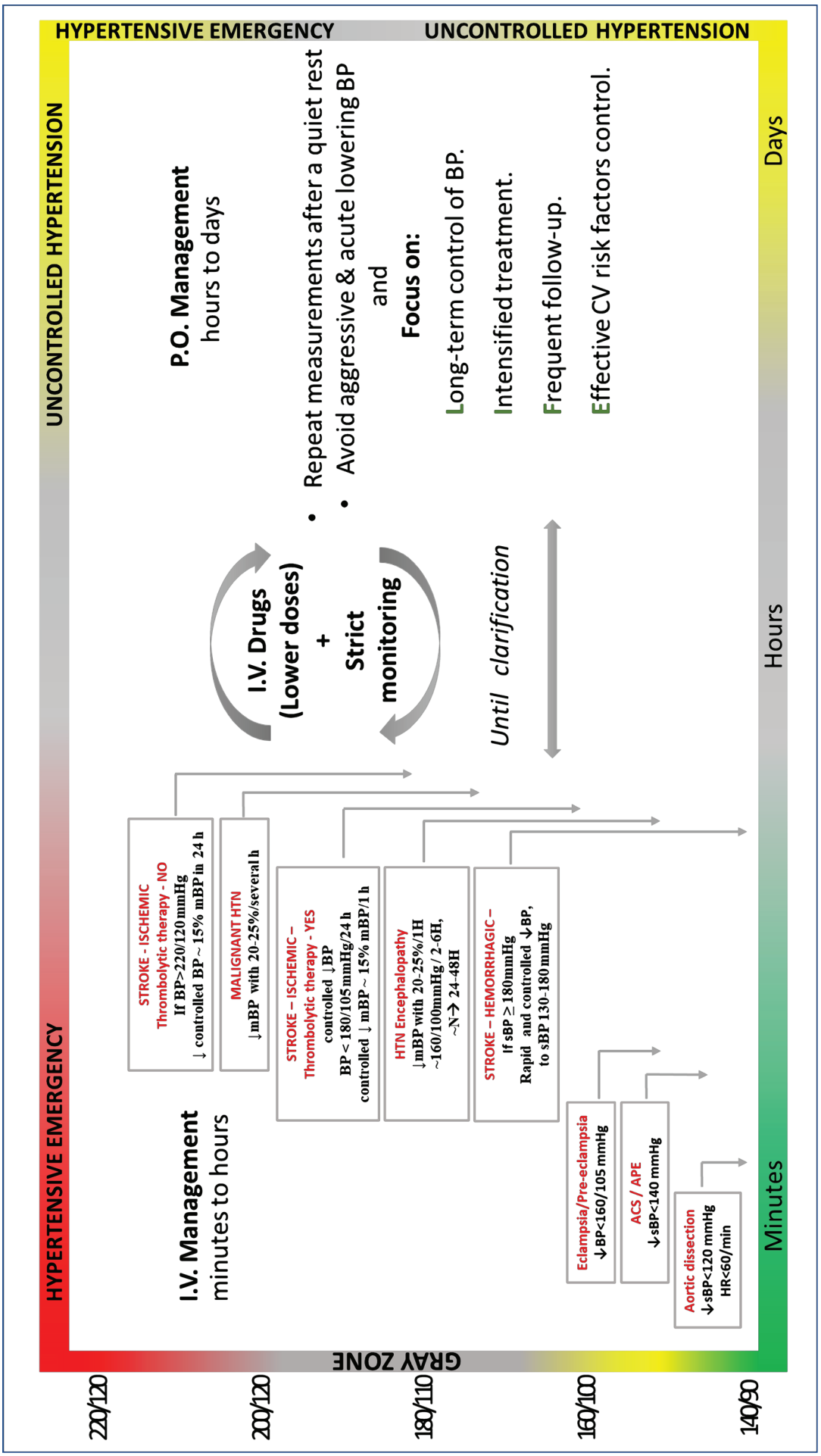

Figure 1. Management of hypertensive emergencies and uncontrolled hypertension – grey zones, timeline and magnitude of blood pressure lowering. ACS – acute coronary syndrome; APE – acute pulmonary oedema; BP – blood pressure; mBP – median BP; sBP – systolic BP; CV – cardiovascular; HTN – hypertensive; iv – intravenous' P.O – per os.

reduction. Providing sustained long-term management for effective cardiovascular prevention should be the goal [25, 28] (Figure 1).

Another observational, cross-sectional study investigated characteristics, and predictors of long-term mortality in patients with UH admitted to ED. Old age, male sex, history of chronic kidney disease, and proteinuria were associated with poor prognostic for all-cause mortality in patients with UH who visited an ED [29].

Hypertensive emergencies

HEs are uncommon presentations, and their long-term prognosis is still a subject of debate. It is not clear if more frequent evaluations and strict monitoring are necessary to reduce the risk of long-term fatal/non-fatal events. Once a patient has a history of HE, his overall risk cannot be improved. History of HE increases the risk of morbidity and mortality, as shown in recent reports [11, 17].

A study that evaluated the incidence of cardiovascular events in patients admitted to the ED with UH and HEs during a mean duration of follow-up of 12±5 months showed that cardiovascular mortality and morbidity were more significant in patients with a previous HE (14.5% *vs.* 4.5% in patients with HE *vs.* UH). Cerebrovascular and renal events were more prevalent in patients with a previous HE event as well [30].

Moreover, F. Saladini *et al.* compared short-term (in-hospital) and long-term (12 months) mortality in patients with HEs and showed that short-term mortality is mainly caused by neurovascular emergencies, whereas cardiovascular emergencies have higher mortality at 12 months [31]. Therefore, current data emphasize the necessity for a better follow-up and management of these patients. Admission to the ED for HEs identifies those patients at increased risk for fatal and non-fatal cardiovascular events; hence, accurate follow-up is mandatory [32].

Data in line with F. Saladini *et al.* study results were seen in the STAT registry. The in-hospital mortality rate was 6.9% (11% for HEs and 0.3% for UH), and deaths were more common in patients with intracranial hemorrhage [33]. In the same study, the authors identified three factors to predict poor prognosis in patients with neurovascular HE: lower minimum BP values, less rebound hypertension, and a higher frequency of neurologic deterioration [5, 31, 33].

Malignant hypertension

Malignant hypertension (MH), the most severe form of hypertension, was originally defined as extremely high BP with a diastolic BP above 130 mmHg and grade III/IV of hypertensive retinopathy. Recently, a new definition was proposed, MH being a group of disorders with out-of-range elevation in BP associated with the concomitant damage of at least three different target organs [34, 35].

In the past, MH had an unfavorable outcome with a mortality rate of around 80% at two years. Despite the overall decrease in mortality rate, the prevalence has been stable for the last four decades [36]. Even if rare, MH still poses a clinically relevant and challenging form of hypertension, and its occurrence should always be considered during the assessment of patients with poorly controlled hypertension [35].

Negative prognostic factors in hypertensive emergencies

Recent epidemiological data show a decrease in mortality of patients with HEs from 80% in 1928 to 10% in 1989 due to the diversity of intravenous drugs that can be administered. However, patients admitted for HEs remain at increased risk of cardiovascular and renal disease compared with hypertensive patients who did not have a HE event [4].

Cardiac troponin I levels

Slightly elevated troponin I (cTni) levels, seen in hypertensive emergencies, may be attributed to a mismatch between oxygen supply and demand or obstructive coronary artery disease (CAD). In a retrospective analysis, patients who presented with a hypertensive crisis were screened by measuring cTnI levels. Results showed that at 2 years, patients with elevated cTnI at presentation had a significantly greater risk of major adverse cardiac or cerebrovascular events (MACCE) and a higher probability of obstructive CAD [37].

Renal impairment at presentation

The kidney plays an essential role in BP regulation through the renin-angiotensin-aldosterone system, and it is an important target in HMOD. Decreased renal function is an established predictor of cardiovascular risk. Incidence and prevalence of cardiovascular events are already significantly higher in patients with mild renal function impairment compared to the general population [38].

Patients admitted with a suspicion of HE and renal impairment at presentation pose the highest

risk for unfavorable evolution. A study conducted by Kumar *et al.* that used a national administrative database and evaluated the incidence, causes, and predictors of 30-day readmission after an episode of HE showed that the most common causes of readmission are HF, hypertension with complications, sepsis, acute kidney injury and stroke [39]. Progressive renal dysfunction is an important threat to patients with MH. Major determinants of long-term renal outcome were initial serum creatinine values and BP control during follow-up [40]. This vicious cycle between hypertension and renal function remains a constant struggle for healthcare providers.

Interestingly, in a small study assessing the histological features of patients with HE-related nephropathy, all 12 patients diagnosed with HE and AKI had an "onion skin" pattern of the arterioles but with no fibrinoid necrosis. In these patients, left ventricular hypertrophy was found on TTE, suggesting chronic high BP values could be the main determinant of renal histological changes as opposed to a predominant acute mechanism. Therefore, strict control of BP can mitigate these patients' poor renal and global prognosis [41]. Similarly, CKD has also been shown to be a cause of uncontrolled BP and an important predictor of HE [16].

Despite the major improvement in 5-year survival in patients with MH, altered renal function at presentation still predicts a worse outcome [35].

Blood pressure variability

Previous studies have adopted mean BP as an indicator of cardiovascular risk, but newer ones are pointing to the variability of BP (BPV) as a potential predictor for outcomes. It has been shown that long-term BPV is associated with a high risk of stroke, coronary events, and target organ damage [42, 43].

Beyond physiological variability in BP, emerging evidence suggests that excessive variability is detrimental and may be associated with increased morbidity and mortality even in acute settings [44–46]. Underlying mechanisms are poorly understood and require further investigations, but some hypotheses include increased intima-media thickening, subclinical atherosclerosis associated with non-adherence to treatment, endothelial dysfunction, and vessel injury induced by shear stress [44].

Currently, there is no clear definition of BPV in acute settings, and data available regarding its importance in the management of acute BP elevations comes mostly from neurological HEs [44]. In the acute setting of neurologic HEs treatment, BPV appears to be a significant predictor of a poor outcome. Some data suggest using calcium channel blockers, such as intravenous nicardipine, to mitigate BPV in patients with intracerebral hemorrhage; however, its impact on clinical outcomes remains largely unknown [46, 47].

In a retrospective cohort study, Preston *et al.* investigated the management of patients with severe acute hypertension (SBP>220 mmHg and/or DBP>120 mmHg) and emphasized the unpredictable and potentially dangerous reduction of SBP using short-acting oral and intravenous (iv) drugs, due to extreme variability of BP [20]. Results were consistent with recent consensus papers and expert reviews that do not recommend using antihypertensive regimens with short-acting oral and iv bolus drugs; instead, it is recommended to focus on better management of the existing treatment.

Discussion and practical conclusion

Acute hypertension disorders are a frequent reason for patients to visit medical care facilities, overburdening the emergency health care system. However, UH remains the main clinical presentation and is a direct consequence of poorly treated or controlled hypertension. Therefore, a focus on better hypertension control and follow-up of ambulatory treated patients should become common practice to prevent short-term and long-term adverse outcomes. For instance, in the short term, patients admitted to ED with UH tend to be overtreated, being exposed to unwanted complications due to excessive lowering of BP. When dealing with UH, it's better to have a gentle approach, to "treat the patient, not the number (BP value)". We suggest using a "focus on life" strategy, meaning focusing on long-term BP control using intensified schemes of antihypertensive treatment with frequent follow-up and effective measures to control cardiovascular risk factors in order to obtain better outcomes (Figure 1).

Accurate diagnosis and risk stratification are the cornerstones in managing patients with acutely elevated BP. True HE represents only a minority of acute hypertensive disorders; hence, one should not initiate rapid lowering BP therapy unless the clinical picture is clearly defined and known to require urgent care.

However, HEs represent potentially life-threatening situations associated with poor cardiovascular outcomes; therefore, a tailored intervention based on the acute HMOD suggested by the clinical and paraclinical profile should be sought. The timeline and magnitude of BP decrease should be designed for the specific patient and his/hers HE in order to avoid adverse outcomes.

Nonetheless, further randomized clinical trials are needed in order to recommend an evidence-based management protocol for HEs.

Conflict of interest

The authors confirm that there are no conflicts of interest.

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