Letter from the Editor-in-Chief

Dear Colleagues,

For many years, this journal has been a vehicle for the delivery of timely and thoughtful information and opinion on the many issues that involve hypertension and cardiovascular risk factors. I would like to thank all my professors, colleagues and sekertarial personnel who served as journal staff and together with the editorial board, and the reviewers to provide the support and feedback necessary to find, develop and publish high-quality material.

In the past 20 years, *The Egyptian Journal of Hypertension and Cardiovascular Risk* has evolved to receive high quality manuscripts from Egyptian authors. Due to some administrative obstacles, we stopped releasing new issues of this journal few years ago. But now, we came back and encourage all authors in Egypt and other countries to support our new release with their valuable work.

Starting with this volume, we've made some significant changes. We've decided to meet the standards set out by the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" developed by the International Committee of Medical Journal Editors (http://www.icmje.org) and have refined our Author Guidelines accordingly. For more information on submitting a paper, please visit the journal's instruction to authors.

The Journal will also strive to achieve rapid publication of all accepted manuscripts. All manuscripts will receive a peer-review decision within 4 weeks after submission and, when accepted, the manuscripts will be published online within 3–4 weeks from acceptance. If authors have a specific publication deadline in mind, please contact our editorial office for a pre submission inquiry. This will enable us to arrange a faster peer review and an even smoother production process. If your manuscript has recently been rejected by one of the top journals in Cardiovascular Medicine due to lack of space, we could expedite a thorough review directly by our editorial board members within 2 weeks, and a rapid publication after its acceptance.

I strongly encourage you to submit your work for consideration for publication in *The Egyptian Journal of Hypertension and Cardiovascular Risk*. An enthusiastic submission requires an energetic and dedicated editorial board to ensure that your article will be reviewed and published rapidly. If you want to join our team by becoming a reviewer for our journal, please let us know by email to **egyptianhypertensionsociety@gmail.com**

Sincerely,

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Hypertension in the Elderly

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Worldwide life expectancy has increased significantly, particularly in industrialized countries. At the beginning of the 20th century life expectancy was between 30 and 45 years. At the end of the century, life expectancy 67 years. The over 80's are the fastest growing group on the planet. In 20 years, the aged population is estimated to exceed almost 20% of the whole population. Hypertension is the leading cause of cardiovascular (CV) morbidity and mortality in adults over the age of 65. The estimated prevalence of HT in the elderly is around 60- 70%. This message will address the following questions:

1. What is the definition of elderly?
2. What are the mechanisms of hypertension in the elderly?
3. What are the clinical and hemodynamic characteristics?
4. What are the challenges in management?
5. Whom to treat, to what target and with which drug class?

Definition of the elderly: old age is officially defined by 60 years according to the United Nations. Sometimes 65 years is used as the cutoff point. While the very elderly is older than 80-85 years.

Mechanisms of HTN in the elderly: 85% of men and women with normal BP at age 55 years will develop HTN after 20-25 years of follow up. There are at least four mechanisms responsible for the higher prevalence of HTN in the elderly, namely increased arterial stiffness, endothelial dysfunction, a proinflammatory state associated with aging and sodium retention. Arterial stiffness develops as a consequence of wall hypertrophy, calcification and atheromatous lesions and changes in extracellular matrix which include an increase in collagen and fibronectin, fragmentation and disorganization of the elastin network.

Endothelial dysfunction resulting in reduction in endothelial- dependent vasodilation secondly to diminished capability to generate NO by the endothelium and decrease of vasodilation receptors. Vascular oxidative stress and inflammation significantly increase with age which results in reduction of NO bioavailability and decreased vasodilator capacity. Sodium retention is more likely in the elderly secondary to progressive deterioration of renal function and reduction in the nephron population.

Clinical and hemodynamic characteristics

These can be both age related and hypertension related changes. Age related changes include reduced cardiac B-receptor mediated responsiveness resulting in tendency for slowed heart rate and decreased heart rate response to exercise. Large artery stiffness leads to impaired activation of the baroreflex.

In the elderly there is a tendency to left ventricular hypertrophy independent of HTN. Also, there is delayed excretion of salt/ volume leading to impaired ability to maintain normal fluid volume. Co-morbid conditions are more common with advancing age and include diabetes mellitus depression, frailty, foot and leg edema, and osteoarthritis.

Hypertension related changes include the greater prevalence of atherosclerotic arterial disease, ischemic cardiac and renal disease, tendency to arrhythmias, abdominal aortic aneurysm, impaired LV function, diabetes and sleep apnea.

Challenges in management

There is a number of conditions that influence the outcome of hypertensive patients and can change the therapeutic strategies. These challenges are the presence of multimorbidity which means the presence of two or more long term conditions in additions to HTN e.g., diabetes mellitus, CAD, dyslipidemia, heart failure, CKD, AF, obesity, OSA, gout and depression. At least two thirds of hypertensive patients have another co-morbid condition. Polypharmacy common in hypertensive patients is associated with poor health outcomes secondary to falls, electrolyte disturbances, hospitalization, heart failure and premature mortality. Frailty, which is reduced physiological reserve leading to increased vulnerability to physical stressors is one manifestation of aging. Tendency to orthostatic hypotension and falls, which are more common in the elderly is another challenge in management. Cognitive impairment is an additional problem in the elderly. The prevalence of dementia in the over 65 population is estimated at 6.5%.

Treatment

A target BP of < 150/ 90 mmHg is recommended to reduce CV morbidity and mortality in the elderly. The recommended BP goal in patients with history of stroke, diabetes or CKD is less than 140/80 mmHg. Individualized decisions are recommended regarding initiation and choice of pharmacologic therapy after trial of dietary approaches. Limiting salt intake and a healthy lifestyle is important. Unless there are specific indications, thiazide diuretics are the first choice.

The choice of therapy is guided by patients' preference and comorbidities. To start low, go-slow approach to medication prescribing is an important approach. The benefits of antihypertensive therapy in reducing hypertensive complications are largely driven by the lowering of BP rather than the choice of drug. On the other hand, CCBs and ACEIs may offer some protection against cognitive decline in older hypertensive patients.

Before starting treatment, BP should be measured first supine followed by upright position to assess orthostatic reaction.

In short, we are expecting to see an increasing member of elderly hypertensive patients in the coming years.

These patients are in need of lifelong treatment. Lifestyle modification and thiazide diuretics are recommended as initial therapy unless there are compelling indications for specific pharmacologic agents.

Mini Review

"Obesity Paradox" Fact or Myth ..?

Azza Farrag, MD, FESC

Over the past several years there has been substantial interest in the so-called 'obesity paradox'. Despite the known association between obesity and mortality in the general population[(1)], numerous studies have reported that obesity confers a survival advantage among patients with cardiovascular disease [(2)].

Meta-analyses have also been published on the obesity paradox [(2-4)], leading some researchers to conclude that the consistency of the data are remarkable.

Actually, obesity worsens almost all cardiovascular disease (CVD) risk factors, exacerbating hypertension, dyslipidemia and increasing insulin resistance. Obesity thus leads to metabolic syndrome and diabetes mellitus and can cause chronic, low grade systemic inflammation.

Not surprisingly, the development of almost all CVD is increased with obesity, including hypertension, coronary artery disease, heart failure, and atrial fibrillation. In addition, patients with obesity who are infected with COVID-19 have endured increased respiratory symptoms, renal injury, coagulopathy, and thromboembolism [(5)], including pulmonary embolism [(6)].

Regarding heart failure, a recent study is the first to look at different ways of measuring the size and proportions of patients, including not only body mass index (BMI), but also anthropometric measurements such as waist-to-height ratio, waist circumference and waist-to-hip ratio, and adjusting the patient outcomes to take account of other factors that play a role in, or predict, these outcomes, such as levels of natriuretic peptide [(7)].

An "obesity-survival paradox" showed lower death rates for people with BMIs of 25 kg/m^2 or more, but this was eliminated when the researchers adjusted the results to take account of all the factors that can affect outcomes, including levels of natriuretic peptides.

The study shows there is no 'obesity survival paradox' when we use better ways of measuring body fat. BMI does not take into account the location of fat in the body or its amount relative to muscle or the weight of the skeleton, which may differ according to sex, age and race. In heart failure specifically, retained fluid also contributes to body weight. Indices that do not include weight, such as waist-to-height ratio, have clarified the true relationship between body fat and patient outcomes, showing that greater adiposity is actually associated with worse not better outcomes, including high rates of hospitalization and worse health-related quality of life.

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Mini Review

Resistant hypertension

Heba El Deeb, MD

Resistant hypertension is defined as persistent elevation of office blood pressure (BP) above the appropriate goal of therapy (>140/90 mmHg in most of hypertensive patients or >130/80 for those with ischemic heart disease, diabetes, or renal insufficiency) despite the use of maximally tolerated doses of three or more different classes of antihypertensive agents, including a diuretic. It is also defined as controlled blood pressure on at least 4 antihypertensive medications. True resistant hypertension should be differentiated from pseudo-resistance hypertension due to suboptimal blood pressure control secondary to medication nonadherence, white coat effect, high salt intake, excess alcohol consumption, uncontrolled obesity, continuous stressful exposure, lack of exercise or poor measurement technique [(1)].

Its true prevalence is <10% of treated patients after exclusion of causes of pseudo-resistant hypertension. Patients are at higher risk of hypertension mediated organ damage, chronic kidney disease, and premature cardiovascular event [(2)].

Diagnosis of resistant hypertension requires ruling out causes of pseudo-resistance hypertension[(1)] and causes of secondary hypertension, as volume overload (due to excessive sodium intake, inadequate diuretic therapy and/or progressive chronic kidney disease) [(1)], drug induced resistant hypertension as nonsteroidal anti-inflammatory drugs, glucocorticoids, estrogen containing contraceptives, sympathomimetics, erythropoietin-stimulating agents, calcineurin inhibitors (cyclosporine, tacrolimus) [(1)]. Renal parenchymal disease which leads to upregulation of renin- angiotensin aldosterone system, increased salt and fluid retention, increased sympathetic nervous system activity and endothelial dysfunction [(3)]. Primary aldosteronism leads to salt and water retention and renal potassium wasting. It is common and often goes undiagnosed, with a prevalence ranging from 8% to 30% [(4)]. Hypokalemia is present in only 9% to 37% of patients who have primary aldosteronism [(4)]. Obstructive sleep apnea is very common in patients with resistant hypertension. It increases upper-airway resistance, leading to hypoxia, and hypercapnia. Screening for it should be common in this population. Renovascular hypertension is a syndrome of elevated blood pressure due to diminished renal arterial blood flow resulting in kidney ischemia [(1)]. It is most commonly caused by atherosclerosis of the renal arteries, but other pathologic processes include fibromuscular dysplasia, renal artery infarct or dissection, and vasculitis. Endocrinopathies include pheochromocytomas and paragangliomas are rare causes of hypertension, accounting for 0.2% to 0.6% of cases, but are associated with significant mortality risk [(5)]. Cushing disease is a relatively uncommon cause of resistant hypertension. Less common disorders include thyroid and parathyroid glands. Testing for primary hyperparathyroidism should be considered in any patient presenting with hypercalcemia [(1)].

Treatment of resistant hypertension includes exclusion of causes of secondary hypertension based on history, physical findings, and individual risk factors. A multifactorial approach to treat resistant hypertension includes a combination of lifestyle modification, pharmacotherapy and using single pill combination treatment is recommended to reduce pill burden and improve adherence to treatment , then identifying comorbidities that require first-line agents that have a compelling indication, such

as beta-blockers for heart failure, history of myocardial infarction, or aortic dissection, or drugs that block the renin- angiotensin-aldosterone system for proteinuria. The initial pharmacologic approach to resistant hypertension consists of 3 medications, each mechanistically different, at maximally tolerated doses, include an ACE inhibitor or ARB, long-acting dihydropyridine calcium channel blocker, diuretic in patients with preserved glomerular filtration rate (GFR), the preferred first-line diuretic is either chlorthalidone or indapamide because of their longer half-life and more potent antihypertensive effect compared with hydrochlorothiazide [(6)]. If blood pressure is still not controlled on maximally tolerated therapy with these 3 agents, a mineralocorticoid receptor antagonist (spironolactone 25-50 mg/d or eplerenone (50 - 100 mg/day) should be the fourth-line agent. The PATHWAY-2 trial demonstrated that spironolactone was superior in reducing blood pressure compared with bisoprolol, doxazosin, or placebo as add-on therapy in patients with resistant hypertension on 3 blood pressure medications [(7)].

The addition of other agents should be based on individual factors, beta-blockers may be the preferred fifth-line agent [(1)]. Other choices include: doxazosin centrally acting alpha-1 antagonist can be used when spironolactone is contraindicated or not tolerated or clonidine, a centrally acting alpha-2 agonist can be given as a transdermal patch to improve adherence, minimize frequent oral dosing, and lower the risk of rebound hypertension [(1)]. If blood pressure is still not at goal, hydralazine may be initiated at a starting dose of 25 mg 3 times a day, with the addition of a nitrate in the presence of heart failure with reduced ejection fraction [(1)]. Finally, minoxidil may be used if hydralazine is not tolerated. Hydralazine and minoxidil are associated with fluid retention and reflex tachycardia [(1)].

Renal denervation to blunt sympathetic tone showed no benefit in the Renal Denervation in Patients with Uncontrolled Hypertension (SYMPLICITY HTN-3) study [(8)]. The Study of the ReCor Medical Paradise System in Clinical Hypertension (RADIANCE-HTN TRIO) [(9)], utilizing a newer catheter design and a stricter medication protocol, demonstrated a decrease of 5.8 mm Hg compared with controls, a modest benefit. Carotid baroreceptor activation therapy and carotid baroreceptor amplification therapy (aimed at sympathetic tone modulation). None of these device therapies are currently FDA-approved, and more studies are needed to determine their long-term efficacy and safety.

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Mini Review

Statin intolerance

Haytham Soliman Ghareeb, MD

Statins are medications that are prescribed to lower cholesterol levels in the body by inhibiting the production of cholesterol in the liver. Statins are considered one of the most effective treatments for reducing the risk of heart attacks, strokes, and other cardiovascular diseases. However, despite their effectiveness, a significant proportion of patients who are prescribed statins experience adverse side effects leading to discontinuation of the medication, a condition known as statin intolerance. This review aims to discuss the types of statin intolerance, their mechanisms, and the current approaches to manage statin intolerance.

Types of statin intolerance

Statins can cause a range of side effects, from mild muscle aches to severe muscle damage and liver toxicity. Statin intolerance can be classified into two categories, namely, muscle-related and non-muscle-related. Muscle-related side effects include muscle pain, cramps, weakness, and myopathy, while non-muscle-related side effects include nausea, abdominal cramping, and diarrhea.

Mechanism of statin intolerance

Statins work by inhibiting HMG-CoA reductase, an enzyme involved in the production of cholesterol in the liver. However, this mechanism of action also affects the synthesis of other molecules that are essential for muscle function, such as coenzyme Q10 and vitamin D. The depletion of these molecules results in muscle damage and weakness, leading to muscle-related adverse events.

In addition, some patients may have a genetic predisposition to statin intolerance due to mutations in genes that regulate the metabolism of statins. For example, a variation in the SLCO1B1 gene has been associated with a higher risk of muscle-related adverse effects.

Management of statin intolerance

The management of statin intolerance depends on the severity of the side effects and the patient's risk factors for cardiovascular disease. For mild muscle-related symptoms, reducing the dose or switching to a different statin may be effective. For severe symptoms, discontinuing the medication and monitoring for muscle damage may be necessary.

Several strategies have been proposed to manage statin intolerance. These include the use of alternative cholesterol-lowering medications, such as ezetimibe, bile acid sequestrants, and PCSK9 inhibitors. These medications have been shown to have similar or better efficacy in reducing cholesterol levels compared to statins.

Furthermore, some studies have suggested that supplementing with coenzyme Q10 or vitamin D may mitigate the muscle-related adverse effects of statins. However, the evidence is not conclusive, and further studies are needed to establish the efficacy of these supplements.

Conclusion

Statin intolerance is a common problem that can limit the effectiveness of statin therapy. Understanding the different types of statin intolerance and their mechanisms can help

healthcare providers choose appropriate management strategies for their patients. While switching to alternative medications is a viable option, more research is needed to identify the optimal management strategies for patients with statin intolerance.

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Original research

A new device (Inferum NBP-050) to correct low blood pressure and to improve symptoms in patients with idiopathic hypotension

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Abstract

Background: Idiopathic hypotension is not uncommon among young individuals. Hypotension could affect quality of life because of anxiety, depression, and low motivation. Many drug- and non-drug therapies are used, yet none is universally recommended.

Aim: was to assess the effectiveness of the Inferum NBP-050 device in correcting blood pressure (BP) in symptomatic hypotensive patients.

Methods: The study included 43 symptomatic hypotensive patients. Demographics and risk factors were assessed at baseline. Symptoms as well as office and ambulatory BP were assessed at baseline and reassessed after 14 days of using the device and then after 3 months. Patients were instructed to use the Inferum device at home on the dorsal surface of their left wrist for 6 minutes, twice daily for 14 consecutive days.

Results: The median baseline office systolic and diastolic BP had increased from 85 to 104.5 mmHg (P<0.001) and from 52 to 66.5 mmHg (P<0.001) respectively at 14 days follow up. Similarly, the median baseline 24-hours ambulatory systolic and diastolic BP had increased from 88 to 103 mmHg (P<0.001) and from 51 to 66 mmHg (P<0.001) respectively. Most patients (88.4%) claimed marked improvement or even disappearance of their symptoms after 14 days of device use. Follow up blood pressure after 3 months showed comparable results to the 14-days follow up results.

Conclusions: The new device Inferum NBP-050 was effective in improving low blood pressure in symptomatic patients with idiopathic hypotension. The effect was apparent after 14 days of device use and it persisted for 3 months thereafter.

Keywords: Hypotension, Blood pressure, Patient care.

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Background

Low blood pressure (hypotension) has never been considered a disease, (1) but rather a manifestation of a disease. Yet, it was noticed that some healthy, non-cardiac individuals, mostly young females, suffer from symptoms of low cardiac output associated with low blood pressure.

There is no absolute cut off levels below which hypotension is diagnosed, rather hypotension is considered when blood pressure drops below the accepted normal blood pressure values with levels below 100/60 mmHg were considered abnormally low. Hypotension is generally regarded as a benign condition and is only considered serious when it affects perfusion of the vital organs (2).

The scientific interest of hypotension is very old yet very little. Low blood pressure is usually associated with physical and psychological symptoms such as tiredness, weakness, dizziness and headache, (3) and with sleep disturbances, anxiety and depression (4). Some studies indicated that low blood pressure is associated with various somatic and psychological symptoms that could influence quality of life and working capacity of humans, often in young age (4-6).

Due to non-specificity of complaints, absence of precise diagnostic criteria, as well as low referral of patients for medical care even in clinically manifested hypotension, actual prevalence of idiopathic hypotension is not clear.

Treatment of idiopathic hypotension involves many non-drug and drug approaches, yet none is specifically recommended. The absence of clear recommendations for patients with idiopathic hypotension invites the search for additional methods of blood pressure correction.

Transcutaneous electro-neurostimulation (TENS) is the application of low frequency electrical impulses through electrodes applied to the skin. It is considered a non-invasive, cheap technique used individually for pain relief (7). TENS has variable effects on the hemodynamics depending on the intensity and the site of application. Inferum NBP-050 device is a new device based on the TENS technique and it is said to have a regulatory effect on vascular tone by means of a non-invasive, transcutaneous, electric current exposure (frequency range 9-77 Hz) on biologically active points MC-6 (on the inner part of the left wrist) and TE-5 (on the outer part of the left wrist) with an exposed zone diameter of 10 mm. The device has 2 programs; program number 1 that provides exposure on point MC-6 and it helps improve cenesthesia for patients with high blood pressure and program number 2 which provides exposure on point TE-5 and helps to improve cenesthesia for patients with low blood pressure. Manufacturers recommend using the device once or twice daily for 10-15 days and they claim that the effect is a long lasting with permanent improvement of the cenesthesia after the initial course of device treatment. The device has been registered as a medical device in Russia and in Europe (8).

The aim of this study was to test the effectiveness of the new Inferum NBP-050 device in improving the low blood pressure in symptomatic hypotensive individuals.

Methods

This study is a prospective, interventional study that included 43 individuals with idiopathic hypotension (defined as low blood pressure (<100/60 mmHg) in absence of an underlying organic disease) who complained of symptoms of low cardiac output. Excluded from the study were individuals with intolerance to electric current, epileptic seizure and neoplasms of any etiology and location. Individuals were recruited over a period of 6 months from public as well as private clinics.

Oral recorded consent was taken from the recruited subjects and the study was approved by the local ethical committee.

Clinical history was taken including age, sex, risk factors assessment (diabetes, smoking, dyslipidemia) and presenting symptoms (headache, fatigue, palpitations, shortness of breath, etc.).

Office blood pressure (BP) was measured according to the standardized technique of blood pressure measurement using a commercially available semiautomated digital device. The systolic and the diastolic BP were measured, and the mean BP was calculated as follows: (mean BP=DBP+1/3 PP) mmHg, where DBP is the diastolic blood pressure and PP is the pulse pressure which equals (systolic-diastolic BP).

A 24-hours ambulatory blood pressure monitoring was done to confirm the low blood pressure levels. The average daytime, nighttime and 24-hour systolic and diastolic blood pressure readings were reported.

The use of the Inferum device

The examining physician taught patients how to use the Inferum NBP-050 device at home. The device looks like a digital wristwatch, and it is worn on the left wrist with the electrodes facing the exposure point TE-5 on the outer part of the wrist. The device is light weight (weighs only 300 gm) and is battery-operated (using 2 alkaline batteries type AAA). Individuals were taught to tighten the cuff of the device around their wrist and to turn on the device by pushing the proper button. The icon on the display should flicker white and this indicates that the device is working. The individuals were instructed to sit still until the flickering stopped, as this meant that the session had ended (the session lasted 6 minutes). When flickering stopped, they were instructed to take the device off and to rest for 20-30 minutes after the session. This session was repeated twice daily for 14 consecutive days (a total of 28 sessions). The electrodes of the device were cleaned and sterilized after each session. Patients were not allowed to use the device after those 14 days.

Follow up symptoms, heart rate, office as well as ambulatory blood pressures were done after 14 days course of the device therapy and 3 months thereafter. Data of follow up and baseline visits were compared. The difference between paired values was calculated as the follow up value minus the preceding visit value.

Statistical analysis

The data were collected, tabulated, and delivered to an SPSS program (version 26) for data analysis. Categorical variables are presented as frequency and percentages and because of non-normality of data, continuous variables are presented as median and range of values. Comparison between paired data was done using a nonparametric Wilcoxon signed rank test. A p-value less than 0.05 was considered significant.

Results

This study included 43 hypotensive individuals, with median age 31 years (range 18-63 years). There were 38 females (88.4%), 1 diabetic patient, 1 current smoker and 6 patients (14%) with dyslipidemia. Analysis of the presenting symptoms showed that patients mainly complained of easy fatiguability (n=13, 30.2%), headache (n=11, 25.6%), fainting attacks (n=9, 20.9%), palpitations (n=4, 9.3%), shortness of breath (SOB) (n=3, 7.0%) and others (n=3).

The baseline heart rate and blood pressure measurements are shown in table 1.

Table 1: Baseline HR and BP measurements (before using the device)

Variable	*Median (Range)*
Heart rate, bpm	87 (73-130)
Office BP	
Office SBP, mmHg	85 (76-100)
Office DBP, mmHg	52 (40-66)
ABPM	
Daytime SBP, mmHg	88 (75-104)
Daytime DBP, mmHg	52 (44-66)
Night-time SBP, mmHg	87 (79-104)
Night-time DBP, mmHg	51 (43-61)
24-hours SBP, mmHg	88 (76-99)
24-hours DBP, mmHg	51 (47-62)

Patients were seen after 14 days of using the device and their symptoms were reassessed. Most patients claimed that their symptoms had improved (n=31, 72.1%) or even disappeared completely (n=7, 16.3%), while other patients complained of persistence of the presenting symptoms (n=5, 11.6%). All individuals were compliant to the 14-days device course, and none complained of any device inconvenience. The values of the office as well as the ambulatory BP after 14 days are shown in table 2.

Almost all patients showed a significantly higher BP readings at follow up, except for 3 patients (2.3%) who showed lower office systolic and diastolic BP and 2 patients (4.7%) who showed lower 24-hours systolic and diastolic BP. The mean arterial blood pressure increased from a median of 63.3 mmHg at baseline to a median of 77.7 mmHg at follow up ($p<0.001$).

Follow up after 3 months of the single device course revealed persistence of BP improvement with no significant difference between the 14-days and the 3-months visits' readings, table 3.

The mean arterial blood pressure increased from a median of 77.7 mmHg after 14-days to a median of 81.3 mmHg at 3-months ($p=0.166$). Figure 1 shows the median of office and ambulatory BP readings at the 3 visits.

Table 2: Comparison between HR and BP measurements at baseline and after 14 days of device use

Variable	*Baseline*	*After 14 days*	*P-value*
Heart rate, bpm	87 (73-130)	77.5 (74-103)	<0.001
Office BP			
Office SBP, mmHg	85 (76-100)	104.5 (74-131)	<0.001
Office DBP, mmHg	52 (40-66)	66.5 (43-80)	<0.001
ABPM			
Daytime SBP, mmHg	88 (75-104)	104 (88-127)	<0.001
Daytime DBP, mmHg	52 (44-66)	67 (52-80)	<0.001
Night-time SBP, mmHg	87 (79-104)	100.5 (85-126)	<0.001
Night-time DBP, mmHg	51 (43-61)	64.5 (46-81)	<0.001
24-hours SBP, mmHg	88 (76-99)	103 (87-127)	<0.001
24-hours DBP, mmHg	51 (47-62)	66 (51-80)	<0.001

Values are presented as median (range).

Discussion

Hypotension is a decrease in blood pressure below the normal values. There is not yet an accepted absolute cut off definition of low blood pressure, and most physicians diagnose hypotension when blood pressure drops suddenly or when blood pressure drop is associated with symptoms of low cardiac output.

Idiopathic hypotension should be distinguished from secondary and orthostatic hypotension. Secondary hypotension is diagnosed when low blood pressure represents a sign of a specific pathological condition as blood loss, cardiac problem, severe allergic reaction, severe infection, and after use of certain medications (9).

Table 3: Comparison between the two follow up visits

Variable	*After 14 days*	*After 3 months*	*P-value*
Heart rate, bpm	77.5 (74-103)	77 (72-104)	0.404
Office BP			
Office SBP, mmHg	104.5 (74-131)	105.5 (94-120)	0.500
Office DBP, mmHg	66.5 (43-80)	69 (58-77)	0.189
ABPM			
Daytime SBP, mmHg	104 (88-127)	103 (93-123)	0.681
Daytime DBP, mmHg	67 (52-80)	68 (60-78)	0.171
Night-time SBP, mmHg	100.5 (85-126)	102 (90-115)	0.477
Night-time DBP, mmHg	64.5 (46-81)	68 (57-77)	0.064
24-hours SBP, mmHg	103 (87-127)	104 (92-117)	0.625
24-hours DBP, mmHg	66 (51-80)	67 (56-95)	0.536

Values are presented as median (range).

In these cases, the treatment of the underlying disease should correct hypotension. Orthostatic hypotension is defined as a drop of at least 20 mmHg systolic and/or 10 mmHg diastolic pressure upon standing or with head-up tilt table test (10). It commonly affects elderly (prevalence may reach 30%) (9) and patients with autonomic dysfunction.

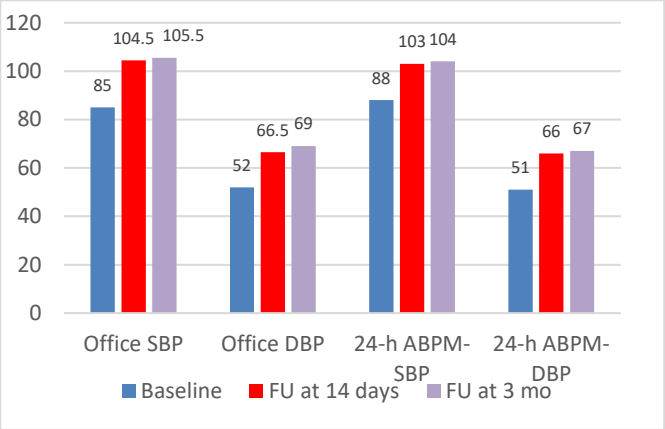

Figure: Comparison between baseline and follow up office and average ambulatory BP measurements.

In contrast, idiopathic hypotension is not considered a disease by itself, (1) and in absence of an underlying pathology, it is not considered a manifestation of another illness. Because of lack of clear diagnostic criteria, idiopathic hypotension is left undefined and poorly investigated and its prevalence is not yet known. A relatively old study by Owens et al (2) used the ambulatory blood pressure monitors to detect hypotensive events in an Irish general population and found that 49% of the included subjects had hypotensive events. They described the profile of those individuals as being mostly females, underweight and with low body mass and low creatinine level.

Despite lack of evidence in literature, hypotension is a common clinical finding in daily practice. (2) Low blood pressure causes many symptoms that could be both annoying and incapacitating to patients. Headache, easy fatiguability, (11) dizziness, syncope and poor perception of self-wellbeing (12) are among the important symptoms of hypotension. When blood pressure is low enough, it could hinder proper perfusion of vital organs and could endanger patient's wellbeing.

Non-drug approaches for hypotension include modification of lifestyle (optimization of sleep/wake regime, balanced nutrition), psychotherapy, high intake of common salt and sufficient amount of fluid, massage of cervical collar zone, acupuncture, physiotherapy (General body conditioning, balneotherapy, hydromassage, neck electrophoresis), physical exercises, wearing of compression stockings as indicated, etc (9).

If the above-mentioned measures are insufficient, drug treatment is initiated: herbal drugs (magnolia vine, aralia, ginseng), midodrine-based drugs, cerebro-protective drugs, antioxidants, vitamin complexes, antidepressants, etc (9). The absence of precise recommendations on management of patients with idiopathic hypotension calls for the search of additional methods for BP correction,

especially in clinically manifested patients. In this context, TENS is known to reduce the severity and incidence of hypotension (13).

The inferum device has been recently released in the market and the manufacturers demonstrated that the device acts through a low-intensity electric current stimulation of peripheral receptors located at the outer surface of the left wrist. Excitation of these receptors lead to a cascade of neurologic stimulation that eventually lead to correction of an abnormal vascular tone and improvement of a low blood pressure. The device is accredited to use in Russia and Europe and is recently allowed in the markets of Egypt (8).

The aim of this study was to investigate the effectiveness of the new Inferum NBP-050 device in correcting hypotension and improving its associated symptoms. In this study, hypotension was defined as an office blood pressure less than 100/60 mmHg with low cardiac output symptoms, in absence of any secondary causes for low blood pressure and/or symptoms.

Forty-three eligible patients were recruited and were given the device to use at home for 14 consecutive days. They were scheduled for a follow up visit immediately after those 14 days and their office as well as ambulatory blood pressures were compared between the 2 visits. Our results showed that 88% of the included patients were females, a finding that was similarly observed in the study by Owens et al (2).

There was a significant improvement of office blood pressure measurements, with 17 mmHg median increase in office SBP and 14 mmHg median increase in DBP. Ambulatory blood pressure measurements showed a similar significant improvement at the follow up visit after 14 days of device use, with16 mmHg median increase in the 24-hours SBP and 13.5 mmHg median increase in the 24-hours DBP. The heart rate showed a significant reduction at follow up, denoting improvement of the hemodynamic mechanisms as well. Most patients (88.4%) claimed that their presenting symptoms had markedly improved or even completely disappeared with the use of the device.

Patients were scheduled for a second follow up after 3 months, without the device and without any treatment. The improvement in blood pressure persisted after 3 months of a single device use, with comparable blood pressure readings in the two follow up visits. Patients also claimed marked improvement in their quality of life with disappearance of disturbing symptoms of hypotension. These results proved that the device exerted its maximum effect on the first cycle of usage and that those effects were maintained on a short-term period.

Limitations

In this study, we only assessed the short-term effects of the device on hypotensive patients (at 14 days and after 3 months of device use). The long-term effects on blood pressure need to be evaluated to validate the use of the device as a therapeutic tool in symptomatic hypotensive patients. It is not clear whether this device could be enough for correction of hypotension or if other drug and non-drug measures are still needed.

Conclusions

The new electrostimulation device (Inferum NBP-050) succeeded in correcting low blood pressure and improving low cardiac output symptoms in a small group of symptomatic hypotensive individuals. The improvement in hypotension was apparent after a single course of device use for 14 consecutive days and the effects persisted for 3 months thereafter. The device was able to correct both the systolic and the diastolic blood pressures and the improvement could be detected by office as well as ambulatory blood pressure monitors.

Further studies are needed for validation of these results.

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Word count: 3385.

List of Abbreviations

BP	Blood pressure
DBP	Diastolic blood pressure
Hz	Hertz
SBP	Systolic blood pressure
SOB	Shortness of breath
TENS	Transcutaneous electro-stimulation

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