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Noninvasive Hemodynamic Monitoring as a Guide to Drug Treatment of Uncontrolled Hypertensive Patients

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TAL TECH PRESS

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Declaration:
Hereby I declare that this doctoral thesis, my original investigation and achievement, submitted for the doctoral degree at Tallinn University of Technology has not been submitted for doctoral or equivalent academic degree.

Anneli Talvik

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signature

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TALLINNA TEHNIKAÜLIKOOL
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Hemodünaamika mitteinvasiivne monitoorimine impedantskardiograafia meetodil ravimresistentse hüpertooniatõvega patsientide ravimivaliku juhtimiseks

ANNELI TALVIK

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KIRJASTUS

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List of Publications

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II FE. Fadl Elmula, P. Rebora, A. Talvik*, S. Salerno, E. Miszkowska-Nagórna, X. Liu, M. Heinpalu-Kuum, T. Comotti, A. C. Larstorp, M. Rostrup, E. Świerblewska, M. G. Valsecchi, S. E. Kjeldsen, M. Viigimaa, K. Narkiewicz, G. Parati, S. Laurent. A randomized and controlled study of noninvasive hemodynamic monitoring as a guide to drug treatment of uncontrolled hypertensive patients. J Hypertens. 2015; 33:2534–2545.

III **A. Talvik**, P. Rebora, M. Heinpalu-Kuum, S. Salerno, E. Miszkowska-Nagórna, X. Liu, T. Comotti, E. Świerblewska, M. G. Valsecchi, FE. Fadl Elmula, A. C. Larstorp, K. Narkiewicz, G. Parati, S. Laurent, M. Viigimaa. Non-invasive hemodynamic monitoring as a guide to drug treatment of uncontrolled hypertensive patients: effects on home blood pressure in the BEAUTY study. Blood Press. 2018 Dec; 27(6):368–375.

*A. Talvik is the joint first author

Author's Contribution to the Publications

Contribution of the author to the papers in this thesis are:

I Collection of data including literature search, data analysis and interpretation, manuscript preparation and revision

II Study design, collection of data including literature search, data analysis and interpretation, manuscript preparation and revision

III Study design, collection of data including literature search, data analysis and interpretation, manuscript preparation and revision

Introduction

Uncontrolled hypertension is a challenging problem all over the world because it often leads to early onset of serious complications and death. Many researchers have studied the underlying reasons for limited success in hypertension treatment despite the wide choice of antihypertensive drugs on the market. One plausible explanation is that patients simply discontinue their treatment because of the side effects. This dissertation investigates a different, emerging hypothesis – that lack of improvement is due to choices of medicines being made without consideration to patient's personal hemodynamics.

Essentially, maintaining blood pressure is not the purpose of the cardiovascular system, but rather the result of its proper functioning. Adequate blood pressure is required for transportation of oxygen-carrying blood to the organs and tissues. Oxygenation of the tissues, in turn, is necessary for the functioning of the organs and the whole body. One of the issues in the clinical management of hypertension is related to the fact that physician-practitioners lack the capacity to measure the underlying hemodynamics, i.e., to determine the causes of elevated blood pressure. Physicians have limited knowledge of the role of hemodynamics in blood pressure management and lack equipment for hemodynamic measurement. In practice, the treatment of the hypertension is based on the only widely available measurable indicator, which is the blood pressure.

The clinical importance of measuring and monitoring hemodynamics is well established, and noninvasive impedance cardiography has been validated as a suitable method to evaluate hemodynamics of the patients with heart disease.

Introducing hemodynamic measurements into physicians' everyday work of treating hypertension calls for more research to establish the procedures and assess its effectiveness, and these are the issues that my thesis aims to bring more light on. The innovative aspect of this work can be summarized as seeking to provide research-based preference for utilizing hemodynamic approach in hypertension treatment as compared to traditional care that is based on elevated blood pressure readings. If the results of the study suggest that incorporating hemodynamic measurement improves hypertension treatment over the traditional care, this opens a whole new way to understand and treat one of the most widespread medical condition.

My doctoral thesis focuses on two questions: 1) Whether measuring hemodynamics with the integrated hemodynamic monitoring system facilitates noninvasive mapping of the hemodynamic status and parameters for patients with drug-resistant hypertension, and 2) Whether integrated hemodynamic management delivers better results along with fewer and less severe side effects in comparison to standard care based on approved treatment guidelines.

This dissertation is especially targeting the issues surrounding blood pressure measurement at home. One of the causes of elevated blood pressure in doctor's office is the "white coat syndrome", presence of which may lead to overtreatment. While the debate around treating the "white coat hypertension" is still ongoing, there is a general agreement that blood pressure values measured at home are important indicators in starting and monitoring the treatment.

In my doctoral thesis I have examined whether treatment accustomed to patient's hemodynamic needs has more positive effect on blood pressure values measured at home than the guideline-based treatment effect on blood pressure, also measured at

home. To study this hypothesis, I used noninvasive integrated hemodynamic management, a device that helps to identify hemodynamic imbalances but has some different characteristics in comparison to other noninvasive impedance methods.

This technique is based on recording changes in the electrical resistance of the chest during heartbeats. These variations are then converted to changes in volume over time and used to derive stroke volume (Woltjer et al., 1997; Osypka et al., 1999; Strobeck et al., 2004; Tang et al., 2009).

We hypothesize that if we could 'tailor' treatment of hypertension so that it is based on the knowledge about individual patient's underlying hemodynamic processes, we would hopefully decrease the side effects that are often the cause of non-compliance with the treatment regimen. Additionally, we expect that this 'tailored treatment', based on patient's hemodynamic profile, will improve hypertension control and decrease complications, such as heart attacks and renal failure.

Abbreviations

ABPM	Ambulatory blood pressure monitoring
ACEI	Angiotensin converting enzyme inhibitor
ADR	Adverse drug reaction
AE	Adverse event
AIx	Augmentation index
ALT	Alanine aminotransferase
ARB	Angiotensin receptor blocker
AST	Aspartate aminotransferase
BB	Beta blocker
BMI	Body mass index
BP	Blood pressure
BSA	Body surface area
CCB-D	Calcium channel blocker – diltiazem
CCB-DHP	Calcium channel blocker – dihydropyridine
CCB-V	Calcium channel blocker – verapamil
CI	Cardiac index
CO	Cardiac output
COPD	Chronic obstructive pulmonary disease
CV	Cardiovascular
CVP	Central venous pressure
DBP	Diastolic blood pressure
DIU	Diuretic
ECG	Electrocardiogram
EDC	Electronic data capture
EF	Ejection fraction
EPCI	Ejection phase contractility index
ESC	European Society of Cardiology
ESH	European Society of Hypertension
HBPM	Home blood pressure monitoring
HR	Heart rate
I	Inotropy
ICG	Impedance cardiography
IHM	Integrated hemodynamic management

IRR	Incidence rate ratio
ISI	Inotropic state index
IV	Intravascular volume
LSWI	Left stroke work index
MAP	Mean arterial pressure
MBP	Mean BP
Non-VD-BB	Non-vasodilating beta blocker
PEP	Pre-ejection period
PP	Pulse pressure
PR	Pulse rate
PROBE	Prospective Randomized Open, with Blinded End-points
PWV	Pulse wave velocity
RR	Respiratory rate
SBP	Systolic blood pressure
SI	Stroke index
SSVRI	Stroke systemic vascular resistance index
SV	Stroke volume
SVRI	Stroke volume resistance index
TC	Total contractility
TEB	Thoracic electrical bioimpedance
TFC	Thoracic fluid content
UCH	Uncontrolled hypertension
VD-BB	Vasodilating- beta blocker
VET	Ventricular ejection time
WHO	World Health Organization

1 HIGH BLOOD PRESSURE

1.1 Signs and symptoms

High blood pressure or hypertension affects approximately one billion people and is the most common cardiovascular disease worldwide.

Blood pressure is determined by two factors: 1) the amount of blood the heart pumps with each beat, and 2) the amount of resistance to blood flow in arteries. The more blood one's heart pumps and the narrower are the arteries, the higher is the resulting blood pressure.

Blood pressure is at its peak at the time the heart muscle contracts and pumps blood into the arteries – a cycle called systole. When the heart relaxes and refills with blood again – a cycle called diastole – the blood pressure decreases.

Conventionally, blood pressure is divided into five categories. An optimal, healthy level for blood pressure is under 120/80 mmHg. Systolic blood pressure between 120 and 129 mmHg and/or diastolic pressure 80–84 mmHg are referred to as normal, systolic blood pressure 130 and 139 mmHg and/or diastolic 85–89 mmHg are referred to as high normal, while systolic pressure readings above 139 mmHg and diastolic pressure 90–99 mmHg are referred to as grade 1 hypertension. When the blood pressure reaches 160/100 mmHg, it is diagnosed as grade 2 hypertension and when above 180 and/or 110 mmHg then as grade 3 hypertension. (Table 1. ESC/ESH, 2018).

Table 1. Classification of office blood pressure and definitions of hypertension grade (ESC/ESH, 2018).

Category	**Systolic (mmHg)**		**Diastolic (mmHg)**
Optimal	<120	and	<80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension	≥140	and	<90

It is quite common that people with high blood pressure display no symptoms at all. If they do, the symptoms of high blood pressure are often non-specific and may only develop when the pressure is already dangerously high. Patients may complain about

headaches, blurred vision, dizziness, tiredness, or other symptoms that are not unique to hypertension.

Hypertension is a major public health issue because of its complications that include such serious conditions as coronary artery disease, heart failure, renal disease, and stroke.

1.2 Causes and risk factors

Hypertension is a result of a complex interaction between genes and environmental factors, and as such, the exact causes of hypertension are not always clear.

Generally, two types of high blood pressure are distinguished: 1) primary hypertension (also referred to as essential hypertension) that develops over many years and there is often no clearly identifiable factor leading to the condition; and 2) secondary hypertension that often starts suddenly and is caused by an underlying condition (including medication). Among various conditions, the common ones are identified in the 2018 ESC/ESH Guidelines for the management of arterial hypertension as following: (Williams et al., 2018)

- Obstructive sleep apnoea
- Renal parenchymal disease
- Atherosclerotic renovascular disease
- Fibromuscular dysplasia
- Primary aldosteronism
- Cushing's syndrome
- Phaeochromocytoma
- Thyroid disease
- Hyperparathyroidism
- Coarctation of the aorta
- Certain medications, such as oral contraceptive pills, herbal remedies, decongestants, over-the-counter pain relievers and some prescription drugs
- Stimulant drugs, such as cocaine and amphetamines

Various lifestyles, conditions and behaviors have been identified as risk factors that can significantly contribute to high blood pressure:

- Overweight
- Physical inactivity, often itself cause of overweight
- Excessive alcohol consumption
- Diet – too much sodium and too little potassium in food
- Stress
- Smoking
- Old age
- Chronic conditions, such as kidney disease, diabetes, and sleep apnea
- Family history of high blood pressure.

1.3 Treatment

In most cases, the first recommendations to patients are changes in lifestyle, such as improving diet, restricting alcohol, and increasing the level of physical activity. While this may be initially sufficient for patients with elevated blood pressure, more advanced stage 1 and 2 patients will also require pharmacological treatment.

Several classes of medications are available for treating high blood pressure, but medicines do not really treat the hypertension but rather help to control it. Most common are diuretics, beta blockers (BB), calcium channel blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers. Choice of antihypertensive drugs is made considering previous experience with the drug, effect of drugs on cardiovascular risk factors, presence of specific disease or disorders, and drug cost, among others (Publication I).

Despite the efforts to educate patients on lifestyle and treatment efforts with antihypertensive drugs, elevated and high blood pressure control rates remain stubbornly low. Some of the reasons why hypertension is poorly controlled are drug intolerance and underestimation of comorbidities, patient non-compliance, physician perceptions about drug effectiveness, cost of medication, etc.

However, the most common cause of uncontrolled blood pressure is inadequate or suboptimal pharmacological treatment, because the antihypertensive drugs are often selected without taking into account the hemodynamic status of the patient (volemia, peripheral resistance, cardiac inotropy, heart rate).

A frequent reason for uncontrolled blood pressure is also poor drug adherence (Gifford, 1988; Klein, 1988; Ceral et al., 2011), which may often be due to side effects induced by drugs (drug-related side effect). Side effects, in particular, may be caused by antihypertensive drugs that have been prescribed but do not match the underlying hemodynamic cause of the high blood pressure (hemodynamics-related side effect) (Fadl El Mula, 2016).

1.4 Resistant hypertension

When a therapeutic *strategy that* a) includes appropriate lifestyle measures, combined with b) a diuretic and c) two other antihypertensive drugs that belong to different classes at adequate doses does not achieve the aim of lowering SBP and DBP values to <140 and <90 mmHg, respectively, hypertension is defined as resistant to treatment (ESH, 2008).

Depending on the population examined and the level of medical screening, the prevalence of resistant hypertension has been found to range from 5–30% of the overall hypertensive population (Mancia, 2013). The true prevalence is more likely to be represented by figures less than 10%. Resistant hypertension is associated with a high risk of CV and renal events (Mancia, 2013; Fagard, 2012; DelaSierra et al., 2011; Daugherty et al., 2012; Persell, 2011).

Early blood pressure control in hypertensives guarantees the best prevention of cardiovascular events on the long term (Fadl El Mula, 2016; 2007 ESH-ESC Guidelines on the Management of Hypertension; VALUE study).

2 HEMODYNAMICS

Hemodynamics is the dynamics of blood flow to organs and ensures transportation of nutrients, oxygen O_2, carbon dioxide (CO_2), hormones, and metabolic wastes to each part of the body with the purpose of maintaining the cell-level metabolism. It embodies the primary task of the cardiovascular system to provide adequate perfusion to all organs.

In response to increased oxygen demand the cardiovascular system of a healthy patient always increases blood flow to his or her organs. However, when the patient is hemodynamically compromised and the system is unable to satisfy increased oxygen demand, the blood flow to organs may be reduced, and in extreme cases, these organs may eventually fail.

Hypertension can be viewed fundamentally as a hemodynamic disorder, presenting with either a hyperdynamic (high cardiac output), vasoconstricted (high systemic vascular resistance), hypervolemic (fluid overload) or chronotropic (effects, that changes heart rate) cause.

Hypertension is a multifactorial disease, but the hemodynamic component of blood pressure physiology includes factors that affect intravascular volume, cardiac inotropy and systemic vascular resistance. In a standard medical setting such as in a primary care office, physicians do not have the ability to evaluate the underlying hemodynamic causes of the hypertension – whether there is hypervolemia, hyperinotropy, vasoconstriction, or a combination of these causes. For this reason, the elevated blood pressure is treated like a symptom, without deeper understanding of the hemodynamic causes of the BP elevation, and the selection of antihypertensive drugs is most often done without the consideration of the hemodynamic status of the patient (Publication I).

When the pharmacological class of the antihypertensive agent does not correspond to the hemodynamic state, blood pressure reduction is limited. By contrast, when the pharmacological class of antihypertensive treatment is adapted to the hemodynamic state (for instance diuretics for hypervolemia, or calcium-channel blocker/ACE inhibitor/ angiotensin receptor blockers for increased peripheral resistances), blood pressure reduction may occur more rapidly and to a greater extent (Publication I; Smith et al. 2005; Sharman et al. 2004; Taler et al. 2002; Badila et al. 2006).

2.1 Hemodynamic monitoring

2.1.1 Invasive hemodynamic monitoring

While clinical measurement of cardiac output, utilizing a flow-directed, thermodilution catheter (also known as the Swan-Ganz catheter) has been available since the 1970s, this type of blood flow measurement is highly invasive and the method represents significant risks to the patient.

The thermodilution technique is the clinical standard for cardiac output estimation, but it requires an invasive and costly procedure, not free from complications. (Mathews et al., 2006, 2008; Reuter et al., 2010; Alhashemi et al., 2011).

Because of this, it has been used only in a very limited subset of high-risk patients who are critically ill, and in whom getting the information about the blood flow and oxygen transport outweighed the risks of the method.

Invasive procedures for hemodynamic profiling are not warranted in outpatient clinics, and noninvasive procedures, such as echocardiography, are costly and operator dependent. (Northridge et al., 1990).

2.1.2 Noninvasive hemodynamic monitoring

Impedance cardiography is a noninvasive technology measuring total electrical conductivity of the thorax and its changes in time to process continuously a number of cardiodynamic parameters, such as stroke volume, heart rate, cardiac output, ventricular ejection time, pre-ejection period and used to detect the impedance changes caused by a high-frequency, low magnitude current flowing through the thorax between additional two pairs of electrodes located outside of the measured segment (Fadl El Mula, 2016) (Fig. 1).

The vital hemodynamic measurements using impedance cardiography could be applicable to significantly more patients, including outpatients with chronic diseases, because it is a safe and low-cost procedure.

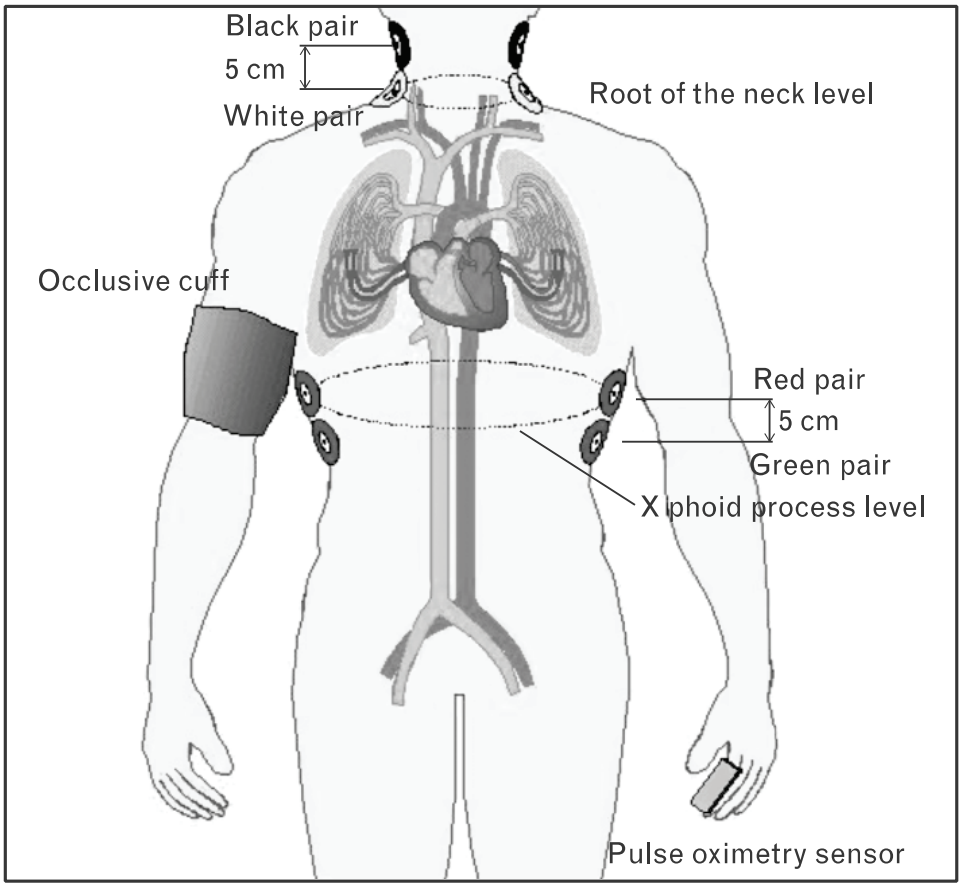

Fig.1 Technique for cardiac impedance management

2.2 Impedance cardiography and hypertension

Impedance cardiography (ICG) is a method to measure hemodynamic abnormalities that has been shown to be both accurate and reproducible (Treister et al., 2005; Van De Water et al., 2003). Impedance cardiography measurements have been used in hypertension to delineate the hemodynamic mechanisms of hypertension (Abdelhammed et al., 2005),

compare age- and gender-related changes in hemodynamics (Alfie et al., 1995; Galarza et al., 1997), and detect the presence of left ventricular dysfunction (Bhalla et al., 2005).

Several studies and one recent meta-analysis (Ferrario et al., 2010) confirmed the value of using impedance cardiography-derived hemodynamic data as an adjunct to therapeutic decision making in the treatment of hypertension.

Most importantly, two randomized controlled studies have demonstrated clinically significant improvement in blood pressure control using ICG-guided therapy (Ferrario et al., 2008). In a single-center trial of patients with resistant hypertension treated in a hypertension specialist clinic, patients in whom therapy was guided by ICG were more likely to receive BB and direct vasodilators, and to receive larger doses of diuretics. These medication differences led to more patients achieving BP control to <140/90 mm Hg (56% vs. 33%) (Taler et al., 2002).

In a multicenter trial of patients with mild-to-moderate hypertension treated in primary care settings, patients in whom therapy was guided by ICG were more likely to receive vasodilating agents when their vascular resistance was high and less likely to receive BB when cardiac index was low. These medication differences led to an 8/7 mm Hg greater BP reduction, greater BP control to <140/90 mm Hg (77% vs. 57%), and greater BP control to <130/85 mm Hg (55 vs. 27%) (Smith et al. 2006). In addition, use of ICG to control BP was shown to be cost effective in both the short- and long-term (Ferrario and Smith, 2006).

A large population-based study of the ability of hemodynamic parameters measured by ICG to define CV risk is currently underway (Chirinos et al., 2006).

ICG is a safe, effective, and cost-effective tool to assist general practitioners treating uncontrolled hypertension.

2.2.1 Impedance cardiography using the noninvasive hemodynamic monitoring system

Compared to classical “impedance cardiography”, which measures cardiac index (CI), stroke index (SI, i.e. SV/BSA), stroke volume (SV), thoracic fluid content (TFC) and stroke volume resistance index (SVRI), the “Hotman®” System has some different characteristics (Fadl El Mula, 2016):

1. It measures SVRI per beat, i.e. SSVRI, an index of vasoactivity, which is not detected by classical systems. While SVRI is calculated as SVRI = 80 (MAP - CVP)/CI, SSVRI is calculated as SSVRI = 80 (MAP - CVP)/SI. Thus, the difference is that the term of equation “(MAP-CVP)” is divided by SI and not by CI. Knowing that CI=SIxHR, the difference between SVRI and SSVRI will occur only when there is a lower than normal SI. Indeed, SVRI can appear normal when an increase in HR compensates for a lower than normal SI, resulting in a normal CI. By using the SVRI parameter, the clinician may not detect the vasoconstriction. By contrast, SSVRI will appear increased in these conditions, and vasoconstriction will be detected by the clinician (Publication III).

2. It is (to my knowledge) the only system which offers a beat to beat evaluation of cardiac inotropy (Publication I).

3. The intravascular volume is not evaluated through TFC (which is subject to an overestimation bias in COPD patients, since it is influenced by any liquid present in the thorax), but calculated as a component of total contractility according to Frank-Sterling Law. Intravascular volume is calculated according to the following equation: total

contractility (TC) = Intravascular volume (IV) + Inotropy (I), so IV = TC - I (where TC is measured through LSWI) (Fadl El Mula, 2016).

Vasoconstriction may be deleterious, in the long term, for target organs, through reduction of oxygen delivery, and ultimately production of radical oxygen species, and less NO availability. The Hotman® System thus provides major parameters for best monitoring the hemodynamic state of hypertensive patients and adapting their antihypertensive drugs, ultimately avoiding chronic underperfusion of target organs.

2.2.2 EXT-TEBCO Module

EXT-TEBCO® is an external module for IBM/PC®-based computers, enabling the user to convert his existing PC/notebook (the host system) into a low cost, noninvasive system for continuous monitoring hemodynamics and for hemodynamic management®.

EXT-TEBCO® contains within its enclosure the TEBCO® printed circuit board (PCB). The host system, which has the Hotman® software installed, receives from EXT-TEBCO® continuously via its COM1 (or other, selectable, COM ports) the hemodynamic, cardiodynamic and respiratory data.

The TEBCO® PCB contains all the circuitry for detection and digital processing of ECG and the TEB signals. The TEB data acquisition is automatic and operator-independent. It also contains an optoisolated communication circuitry with the host system. From these ECG and TEB signals, acquired continuously and noninvasively, EXT-TEBCO® processes and sends to the serial port COM1 of the host system the digital values of important cardiodynamic and respiratory parameters and four digitized analogue signals.

EXT-TEBCO® connects to the patient via a special, 3 m (10 ft) patient cable and four pairs of HSI® disposable, solid gel electrodes, placed on each side of the patient's neck and lower thorax. (Fig. 2).

A patient's BP has to be periodically measured with any sphygmomanometer (manual, semiautomatic or automatic). The operator enters the measured systolic and diastolic blood pressure values via the host system's keyboard.

From the cardiodynamic data provided continuously by EXT-TEBCO® and the blood pressure values entered manually, the host system (with the Hotman® software) processes complete hemodynamics of a patient and displays it in real-time.

In addition, the system provides the hemodynamic management information.

The nine cardiodynamic parameters and one respiratory parameter transmitted to the host system are presented in Table 2.

Table 2. Parameters transmitted to the host system, which has the Hotman® software installed (HOTMAN Operator's manual).

HR	*Heart Rate*	(beats/min)
VET	*Ventricular Ejection Time*	(sec)
PEP	*Pre-ejection Period*	(sec)
TFC	*Thoracic Fluid Conductivity*	(Ω^{-1})
EPCI	*Ejection Phase Contractility Index*	(sec^{-1})
ISI	*Inotropic State Index*	(sec^{-2})
EF	*Ejection Fraction estimate*	(%)
SI*	*Stroke Index*	(ml/beat/m^2)
CI*	*Cardiac Index*	(l/min/m^2)
RR	*Respiratory Rate*	(breaths/min)

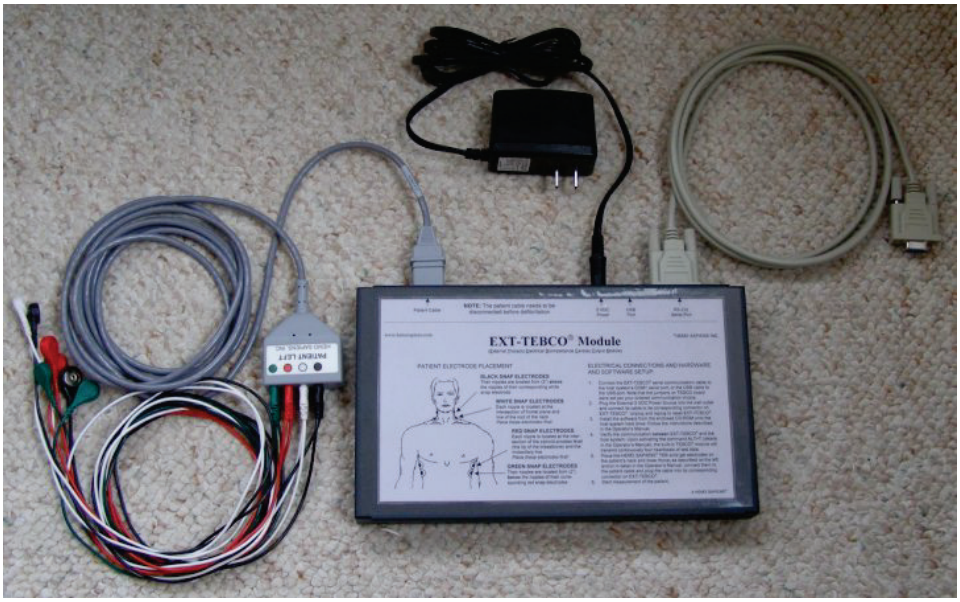

*Fig. 2 **"Ext**ernal **T**horacic **E**lectrical **B**ioimpedance **C**ardiac **O**utput **Module**"*

(Publication I)

3 AIMS OF THE THESIS

This doctoral thesis seeks to improve the treatment of uncontrolled hypertension by testing the effects of noninvasive monitoring of hemodynamic parameters and using impedance-cardiography-guided therapy on patients with uncontrolled elevated blood pressure.

The thesis has four aims:

1. To evaluate hemodynamic modulators and subsequent hemodynamic status in patients with uncontrolled hypertension.

2. To investigate whether utilizing noninvasive monitoring of hemodynamic parameters combined with a drug selection algorithm (integrated hemodynamic management – IHM) improves uncontrolled hypertension compared to the conventional drug selection.

3. To study whether utilizing noninvasive monitoring of hemodynamic parameters combined with a drug selection algorithm (integrated hemodynamic management – IHM) reduces side effects compared to the conventional drug selection.

4. To investigate whether utilizing noninvasive monitoring of hemodynamic parameters combined with a drug selection algorithm (integrated hemodynamic management-IHM) compared with conventional drug selection may improve home blood pressure in patients with uncontrolled hypertension.

4 PATIENTS AND METHODS

In April 2007, the ESH Scientific Council approved 65 Hypertension Excellence Centers, representing 13 European countries. The list of ESH Hypertension Excellence Centers was published in the journals endorsed by the ESH (Journal of Hypertension and Blood Pressure) and displayed on the ESH Website (www.eshonline.org) (Viigimaa et al., 2008).

Patients aged 18–85 years of either gender were referred to the university outpatient clinics in the European Hypertension Excellence Centers from general practices. The final sample included 134 patients with essential hypertension who had been treated with at least two antihypertensive drugs (Publication I).

A clinical evaluation was conducted in nine centers over a period of 2 months, using a common standardized procedure. According to the protocol, any patient meeting inclusion and exclusion criteria attended each Center of Hypertension over the study period was chosen to be evaluated. All patients were already following an antihypertensive treatment, but their hypertension was not controlled under the previous medication (BP values >140/90 mmHg clinically and >130/80 mmHg average of 24 h on ambulatory BP monitoring) (Publication I).

Office BP was taken in concordance with "2007 ESH Guidelines for the management of arterial hypertension", with the patient seated using an oscillometric method. TEB measurement was obtained as a part of routine care. Hemodynamic parameters were achieved in supine patients after 10 min of rest.

4.1 STUDY: BEtter control of blood pressure in hypertensive pAtients monitored Using the HOTMAN® sYstem (BEAUTY study) (Publication II, III)

This was a multicenter prospective randomize parallel groups, "Hotman-driven" therapeutic approach, PROBE design study, comparing the reduction in daytime SBP- ABPM over 6 months in 2 groups: one group (Co-Group) received usual antihypertensive care according to the 2007 ESH Guidelines, and one group (group IHM) according to the results of the noninvasive hemodynamic monitoring.

A clinical evaluation was conducted in five European Hypertension Excellence Centers: Gdansk (Poland), Milan (Italy), Oslo (Norway), Paris (France) and Tallinn (Estonia), over a period of 2 months, using a common standardized procedure (Publication III).

Patients aged 18–85 years of either gender were referred from general practices responding to letters of invitation or were recruited directly by newspaper advertisements or referrals to the university outpatient clinics (Publication III).

The final sample included 167 patients with UCH who had been treated with at least two antihypertensive drugs. According to the protocol, any patient meeting inclusion and exclusion criteria and attending each Center of Hypertension over the study period was chosen to be evaluated. All patients were already following an antihypertensive treatment, but their hypertension was not controlled under the previous medication: BP values 140/90 mmHg clinically (Publication I). Additionally, patients had to qualify by also having mean ambulatory daytime SBP at least 135 mmHg. Prior to the qualifying ABPM, drug treatment was unchanged for two weeks and no other change in medication was pre-planned for the following 6 months (Fadl El Mula, 2016).

Office BP was taken in concordance with "2007 ESH Guidelines for the management of arterial hypertension", with the patient seated using an oscillometric method (Publication I).

Home BP was available in 46 IHM and 38 controls at the beginning of the study and at 6 months. Home BP was measured for one week before study visit. Home BPM was done according to the 2008 European Society of Hypertension (ESH) home BP monitoring guidelines (Publication III).

Home BP measurements were not performed on all patients in the study due to shortage of devices in some centres and due to home BP being a secondary endpoint and not obligatory in the protocol (Publication III).

The study, at each of its five sites, was monitored by Sintesi Research (Milan, Italy), an independent Clinical Research Organization specialized in Clinical Trials Management which offers full support in planning, running and reporting Phase I-IV Clinical Trials (https://www.sintesiresearch.com/). Sintesi Research also assembled all the baseline and follow-up data collected in five sites, such as of patient characteristics, office BP, home BP, ABP, and IHM.

The data was cleaned prior to transfer to the central database at Istituto Auxologico Italiano, Department of Cardiology, Milan, Italy, and was locked prior to any statistical analysis.

We implemented the HOTMAN® System (Hemo Sapiens Inc.), a computer operating device based on TEB for providing noninvasive assessment of hemodynamic modulators and evaluation of the hemodynamic status of the patients. TEB measurement was obtained as a part of routine care. Hemodynamic parameters were achieved in supine patients after 10 min of rest. The TEB technique belongs to impedance cardiography (ICG), a noninvasive hemodynamic diagnostic and monitoring technology. ICG has demonstrated its usefulness and reproducibility in various populations (Publication I; Neath et al., 2006; Van der Water et al., 2003; Thangathurai et al., 1997; Abdelhammed et al., 2005).

The principle of TEB is based on measuring the thorax impedance (resistance of body tissues) when is applied an alternating current with a very low intensity and high frequency. The measurement current passes between two pairs of TEB sensors located on the upper neck and upper abdomen in a direction parallel to the spine. Four other receptor sensors are located at the root of the neck and at the diaphragm level. These sensors detect ECG signals as well as the voltage of the electrical current that crosses the thorax, which is proportional to the thoracic impedance (Publication I; Sramek, 2002).

Noninvasive hemodynamic monitoring is based on a proprietary very low TEB technology, utilizing very low TEB measurement current with fully digitized, high sampling rate generation and acquisition of the TEB signal. The TEB measurement current is only 7 μA, safe for the patients and with high reproducibility. Its digital data processing results in wide bandwidth, high-quality and high-resolution TEB signal, unavailable with analogue acquisition methodologies (Publication I).

These features enable precise measurements of TEB signal's key magnitude and timing events. Following the digital process of TEB and ECG signal, this technique provides information about the value of blood flow [cardiac index (CI) and SI, heart rate (HR)], contractility and left ventricle performance [ejection phase contractility index (EPCI), inotropic state index (ISI) and left stroke work index (LSWI)] and afterload [stroke systemic vascular resistance index (SSVRI), and thoracic fluid conductivity (TFC)].

Compared with the classical ICG technique, the Hotman® System has some different characteristics: it measures systemic vascular resistance per beat as SSVRI, a parameter not detected by other bioimpedance devices; it is the only system that offers a beat-to-beat evaluation of cardiac inotropy (ISI); and intravascular volume is not

evaluated through TFC, but calculated as a component of total contractility according to the Frank–Sterling Law. In addition, the Hotman® System presents the hemodynamic status of the patient and the situation of the hemodynamic modulators: volemia, inotropy, vasoactivity and chronotropy (Publication I; Badila et al., 2006; Hotman® Operators manual, 2011).

4.2 Statistical analysis

All statistical analyses were performed by professional independent medical statisticians (P.R., X.L., M.G.V.) at the University of Milano-Bicocca.

Power analysis showed that each group needed at least 108 participants. It is recommended to enrol 250 patients and randomize 125 participants per group in order to end up with 108 individuals per group to detect a different decrease of ambulatory daytime SBP from baseline to study end between IHM and classical drug selection group.

Descriptive statistics, including means, standard deviations, and frequencies, were used to summarize patients' characteristics. Characteristics of patients with and without HBPM were compared with Chi-square test and t-test for categorical and continuous variables, respectively (Publication III). For efficacy analyses, we used full analysis set that included all randomized individuals who had the assessment of the primary endpoint. For safety analyses, a set with all randomized individuals who had at least one safety assessment at a follow-up visit.

We used the two-sample t-test to analyze the group differences of the primary endpoint – the ambulatory SBP change. The SBP change was SBP at month 6 minus baseline (negative means decrease) and their 95% confidence intervals. The secondary endpoints on efficacy were similarly evaluated using the two-sample t-test on BP changes and chi-square test for the percentage of normalization of BP.

The number of adverse events in each group was compared by a Poisson model, taking into account the total follow-up times (Fadl El Mula, 2016). We computed the incidence rate ratio between IHM group and control group on overall adverse events, serious adverse events, drug- related adverse events, and the severity of adverse events.

The difference among the two arms on HBPM, ABPM and OBPM were evaluated using two-sample t-test on BP changes from baseline to follow-up. Chi-square test with one degree of freedom was used to compare the percentage of normalization of BP.

A linear regression model on HBPM and ABPM at follow-up month six (M6), adjusting for the baseline home SBP, was applied to account for centers and potential risk factors (sex, age, BMI) in the estimate of treatment effect. Rate of BP decrease in OBPM was analyzed separately by a longitudinal analysis. A mixed model was applied including (as response variable) all the BP measurements available from baseline to M6 for each patient on the secondary analysis set, with at least two measurement available and assuming missing at random (Publication III). The model included number of visits, group id, the interaction between the group and visit number as dependent variables (Publication III).

The chi-square test was used to compare the distribution of type of antihypertensive drugs (classified as agents acting on the renin–angiotensin system, b-blocking agents, CCBs, diuretics and others) at the study end (Fadl El Mula, 2016).

5 RESULTS AND DISCUSSION

5.1 Identification of the hemodynamic modulators and hemodynamic status in uncontrolled hypertensive patients (Publication I)

The purpose of the study was to assess hemodynamic modulators (intravascular volemia, inotropy and vasoactivity) and hemodynamic status [mean arterial pressure (MAP) and stroke index (SI)] in uncontrolled hypertensive patients using a noninvasive thoracic electrical bioimpedance (TEB) technique (the Hotman® System, Hemo Sapiens Inc.) and possible relationship between uncontrolled hypertension and untargeted hemodynamic modulators (Publication I).

A number of 134 uncontrolled hypertensive patients with essential hypertension were evaluated in nine European Hypertension Excellence centers by means of TEB (the Hotman® System).

During the study, office systolic and diastolic BP averaged 156/91.9 mmHg; 110 subjects (82.1%) had BP level above normal values and 24 (17.9%) patients exhibited normal BP (Publication I).

Hemodynamic measurements show that almost all patients (98.5%) presented at least one altered hemodynamic modulator: intravascular hypervolemia (96.4%) and/or hypoinotropy (42.5%) and/or vasoconstriction (49.3%).

Among the whole study group, 70 (52.2%) patients were diagnosed as normodynamic (SI in normal range: 35–65 ml/m^2), 36 (26.9%) as hypodynamic (SI 35 ml/m^2) and 28 (20.9%) as hyperdynamic (SI 65 ml/m^2). Hemodynamic state is defined by MAP and blood flow (SI) over one heartbeat interval.

During the noninvasive hemodynamic assessment, six different hemodynamic states were found: hypertension and hypodynamic in 30 (22.4%) patients, hypertension and normodynamic in 54 (40.3%) patients, hypertension and hyperdynamic in 18 (13.4%) patients, normotension and hypodynamic in six (4.5%) patients, normotension and normodynamic in 16 (11.9%) patients and normotension and hyperdynamic in 10 (7.5%) patients (Publication I) (Fig 3).

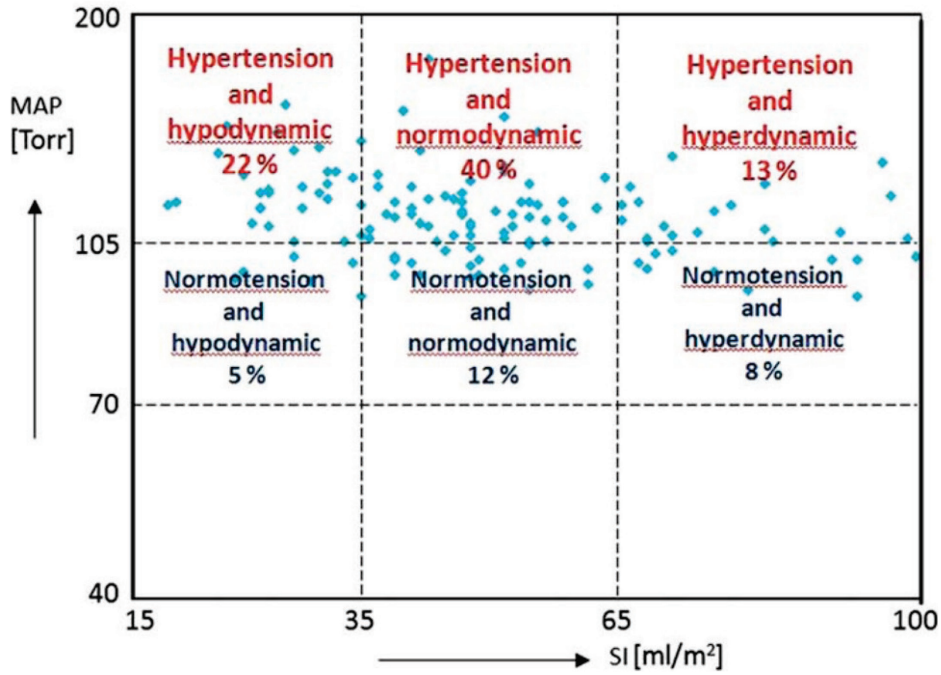

Fig 3. Scattergram of hemodynamic state of all patients measured in the study with superimposed percentage of correspondent hemodynamic states. (Publication I)

From these six hemodynamic states, hypertension occurred in more than 76% of patients and less than 12% reached the hemodynamic goal, being simultaneously normotension and normodynamic.

Hypertension in any individual is caused by its specific and unique contribution of abnormal levels in hemodynamic modulators. Hemodynamic measurements revealed that most of patients presented intravascular hypervolemia (96.4%), and/or hypoinotropy (42.5%) and/or vasoconstriction (49.3%).

The initial hemodynamic assessment showed the following distribution of the hemodynamic modulators (intravascular volemia, inotropy and vasoactivity), including chronotropy: hypovolemia two (1.5%) patients, normovolemia three (2.2%) patients, hypervolemia 129 (96.3%) patients, hypoinotropy 57 (42.5%) patients, normoinotropy 58 (43.3%) patients, hyperinotropy 19 (14.2%) patients, vasodilation nine (6.7%) patients, normovasoactivity 59 (44%) patients, vasoconstriction 66 (49.3%) patients, hypochronotropy 55 (41%) patients, normochronotropy 50 (37.4%) patients and hyperchronotropy 29 (21.6%) patients (Publication I). (Fig 4).

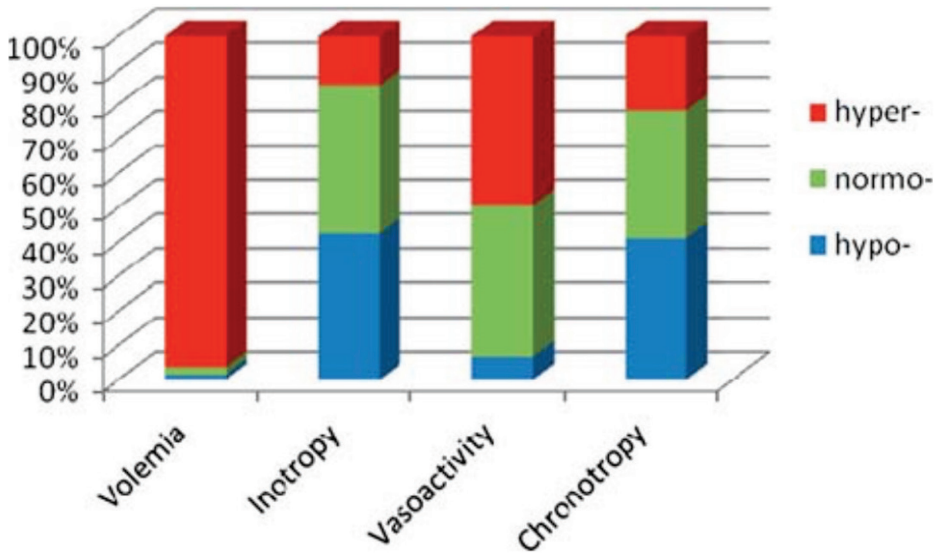

Fig. 4. Hemodynamic modulators distribution. (Publication I)

An abnormal hemodynamic state is a result of abnormal levels in one or a combination of hemodynamic modulators. Since any single abnormal hemodynamic modulator (intravascular volume, inotropy and vasoactivity) might be responsible for a hemodynamic disturbance, we divided the study population into four subgroups according to number of altered hemodynamic modulators: (I) all three hemodynamic modulators altered (44.8%), (II) a combination of two altered hemodynamic modulators (22.4%), (III) one hemodynamic modulators altered (31.3%), and (IV) no hemodynamic modulators altered (1.5%) (Publication I). (Fig 5).

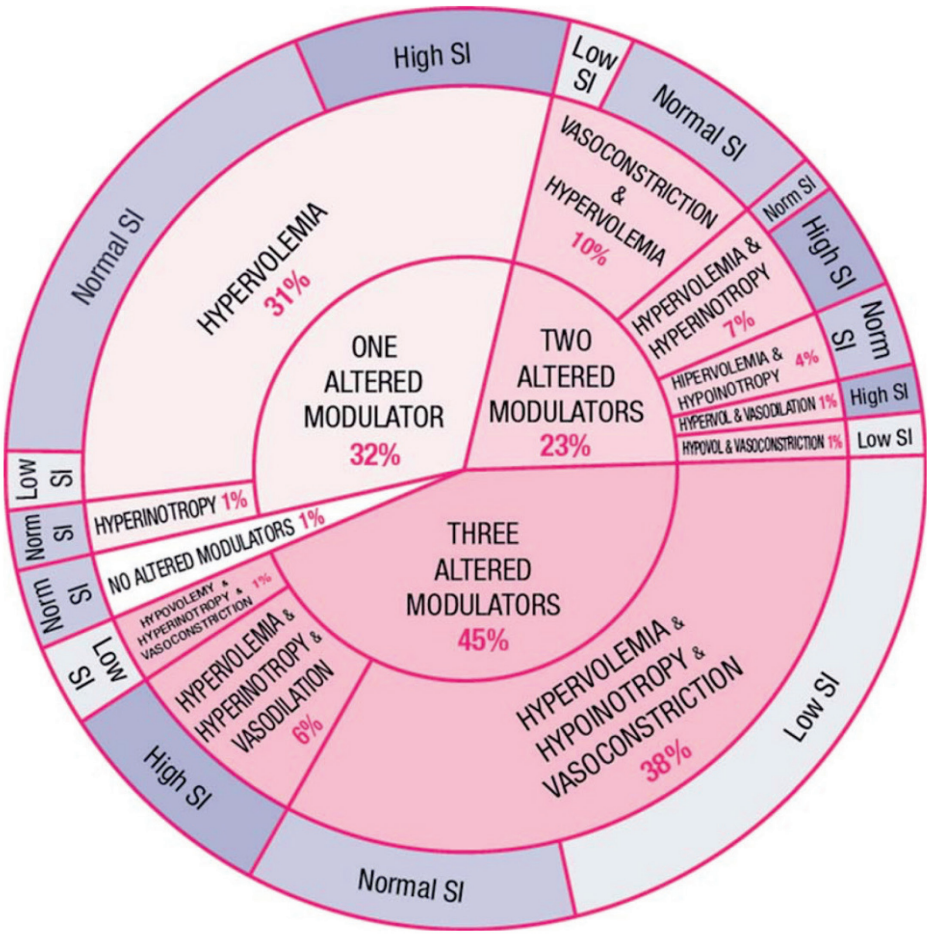

Fig. 5. Subgroup distribution according to number of altered modulators. (Publication I)

The subgroup of patients with three altered hemodynamic modulators was the most numerous (44.8%) in the study population. That subgroup included three different combinations of altered modulators, as Figure 5 shows. In fact, the patients with concomitant hypervolemia hypoinotropy vasoconstriction represent the biggest homogenous population in the study group. Despite a similar combination of altered modulators, in this group there were 34 patients found as hypodynamic (low SI value) and 17 were found as normodynamic. (Publication I).

A combination of two altered hemodynamic modulators was met in 30 (22.4%) patients, and contains five pairs of different altered hemodynamic modulators:

Hypervolemia and vasoconstriction,
hypervolemia and hyperinotropy,
hypervolemia and hypoinotropy,
hypervolemia and vasodilation,
hypovolemia and vasoconstriction.

Almost one third of total study patients (31.3%) belonged to the subgroup with one hemodynamic modulator altered. With one exception, this altered hemodynamic modulator was hypervolemia. Again, SI values varied broadly despite similar hemodynamic modulator altered. Only two patients exhibited normal values for all hemodynamic modulators. This is an interesting finding considering a total of 24 patients with normal BP, because the remaining 22 patients showed normal BP but still abnormal hemodynamic profile (Publication I).

The primary function of our CV system is not a generation of BP but a delivery of oxygen to all tissues. Oxygen delivery is a phenomenon related to the blood flow and not to BP. Actually, an adequate delivery of oxygen to all organs under all metabolic conditions is the true definition of CV health. In this respect, cardiac output is the ultimate expression of CV performance (Publication I; Bonow et al., 2008).

A healthy CV system maintains adequate supply of oxygen to all tissues under all metabolic conditions by a dynamic variation of levels of four modulators. Three of them are the systemic hemodynamic modulators (intravascular volume, inotropy and vasoactivity) and one is the perfusion flow modulator (chronotropy) (Publication I; Ferrario et al. 1978; Davidson et al., 2003). The body changes the levels of these four modulators for every heartbeat in response to a varying oxygen demand of all tissues (Publication I; Sramek, 1995).

The study population shared six hemodynamic states (pairs of MAP and SI) with different needs in term of treatment in order to achieve the goal of normotension and normodynamism. This situation reflected the total contribution of actual treatment over MAP (76% still exhibiting hypertension) and SI. Different combinations of altered hemodynamic modulators were met in study subjects (Publication I)

One major problem that should be reconsidered in the treatment of hypertensive patients is the use of drugs at the correct and most effective dosages. Another problem is that BP elevation is treated like a symptom, without paying attention to the hemodynamic causes. Physicians mainly neglect the other hemodynamic parameters like cardiac output, left ventricle contractility and vascular resistance, despite the fact that used drugs are modifying the entire hemodynamic status. This could be an explanation for the relatively low BP control rates and important associated side-effects (Publication I).

Thoracic bioimpedance provides the clinician with reliable hemodynamic information that could only previously be obtained in the critical care unit of a hospital using a pulmonary artery catheter. Implementation of this hemodynamic information aids in identifying the hemodynamic components of hypertension, allowing the initiation and titration of medications that act more effectively. In conclusion, our data suggest a strong relation between hypertension and abnormal hemodynamic modulators, with significant individual variation of the hemodynamic profile. Careful analysis of all hemodynamic modulators could precede pharmacological treatment modification in order to achieve a normohemodynamic status (Publication I).

5.2 Noninvasive hemodynamic monitoring as a guide to drug treatment of uncontrolled hypertensive patients (Publication II)

The purpose of the present study was to examine the clinical usefulness of IHM by measuring thoracic impedance in making the choice of drugs in improving BP control in people with UCH without getting mixed up with the controversy regarding 'treatment resistant hypertension' (Fadl El Mula, 2016). We have used prespecified inclusion and exclusion criteria in order to include a homogenous population suitable for the aim of the study. We aimed to test this hypothesis through use of a novel device for noninvasive monitoring of hemodynamic parameters combined with a predefined algorithm of drug selection.

In short, this procedure aimed at tailoring the antihypertensive treatment to the underlying hemodynamic aberration such as increasing the dose of diuretic in volume overloaded patients or prescribing or increasing the dose of vasodilatory medicines in patients with high peripheral resistance, and decreasing the dose of BB or nondihydropyridine calcium-channel blockers in the presence of hypoinotropy (Fadl El Mula, 2016; Taler et al., 2002; Faini et al., 2014).

<table>
<tr><th>Hemodynamic status</th><th colspan="4">Antihypertensive drug</th></tr>
<tr><td>Vasoconstriction</td><td colspan="2">If +34 to +100%, then use normal dose of CCB-DHP, ACEI, ARB</td><td colspan="2">If > +100%, then use high doses of CCB-DHP, ACEI, ARB</td></tr>
<tr><td>What to do</td><td colspan="4">In each case:
-if inotropy > +20%, then use CCB-DHP
-if inotropy is normal (-20% to +20%) or low (i.e. hypo-inotropy, less than –20%), then use ACEI or ARB</td></tr>
<tr><td>Hypervolemia</td><td colspan="2">If normal (-20 to +20%), then no DIU</td><td colspan="2">If high (> +20%), then use DIU</td></tr>
<tr><td>What to do</td><td colspan="2"></td><td>If +20 to +50%, then use normal dose of DIU</td><td>If > +50%, then use high dose of DIU</td></tr>
<tr><td>Hyperinotropy</td><td colspan="2">With normal volemia</td><td colspan="2">With DIU-induced hypovolemia (< –20%)</td></tr>
<tr><td>What to do</td><td>If +20% to +60%, then use VD-BB</td><td>If > +60%, then use non VD-BB</td><td colspan="2">Stop DIU,
Add CCB, ACEI or ARB
Do NOT prescribe BB</td></tr>
<tr><td>Hypoinotropy</td><td colspan="4">Stop BB
Prefer CCB-V or CCB-D rather than CCB-DHP</td></tr>
</table>

Fig. 6 Scheme for selecting and titrating antihypertensive drugs. (Publication II)

Adjustments of drug treatment, which could be done by changing either class of medication or their doses, were then performed in the IHM group under the guidance of a prespecified algorithm according to patients' vascular resistance, volemia and/or inotropy (Publication III). (Fig. 6).

Adverse events were regularly investigated actively at each visit, by giving participants a written self-questionnaire in which 30 common adverse events related to antihypertensive drugs were proposed in a neutral order for the purpose of catching the data (Fadl El Mula, 2016).

Mean daytime SBP by ABPM changed from 150.3 ±11.6 and 149.9 ±11.4 mmHg at baseline to 134.5 ±12.0 and 134.5 ±12.5 mmHg at study end in IHM and control group, respectively, with no difference (d) between the two groups, d = –0,38, 95% confidence intervals = (–5.00, 4.25), P = 0.87. The linear regression model adjusting for baseline SBP, recruiting center, age, sex and BMI confirmed no difference between the two groups in ambulatory SBP at 6 months (SBP IHM-control = –0.29, 95% confidence intervals = (–3.90, 3.32) mmHg, P = 0.87) (Publication III).

Mean office SBP changed from 158.5 ±19.9 and 155.1 ±15.0 mmHg at baseline to 137.3 ±15.5 and 137.9 ±14.2 mmHg at study end in IHM group and control group, respectively, *d* = –4.03, 95% confidence intervals = (–9.83, 1.78), *P* = 0.17. No between group difference in ABP and office BP changes between baseline and month 6 was found statistically significant (Publication III).

The analysis of safety included 80 and 81 patients from IHM and control group, respectively. The mean number of adverse events in IHM and control group was compared, the IRR was 0.63 (95% confidence intervals: 0.45–0.89, P = 0.008) for total adverse events and 0.62 (95% confidence intervals: 0.41–0.93, P = 0.021) for drug-related adverse events, indicating a lower number of adverse events in IHM than in controls, as presented in Table 3 (Publication II).

Table 3. Mean number of adverse events in safety analysis set (Publication II).

Type of adverse event	IHM group Mean (SD)	Control group Mean (SD)	Poisson model IRR* (95%CI)	Poisson model *P* value
No. of overall adverse events	1.18 (1.17)	1.91 (2.09)	0.63 (0.45–0.89)	0.008
No. adverse events of endpoint special interest**	0.31 (0.61)	0.31 (0.54)	1.04 (0.59–1.84)	0.896
No. drug-related adverse events	0.74 (0.96)	1.22 (1.66)	0.62 (0.41–0.93)	0.021
No. serious adverse events	0.11 (0.36)	0.23 (0.58)	0.49 (0.20–1.17)	0.110
No. severe adverse events	0.05 (0.22)	0.04 (0.19)	0.99 (0.61–1.63)	0.979

*IRR, incidence rate ratio.
**Endpoint special interest includes atrial fibrillation, myocardial infarction, palpitations, tachycardia, chest pain, edema, increased serum creatinine, gout, hyperkalemia, syncope, renal impairment.

Result show that there were fewer side-effects in the IHM group than in the control group, including drug-related side-effects.

Table 4. Overall number of side-effects as listed according to the questionnaire in the protocol (Publication II).

Adverse event	Randomization Group		All
	IHM group	Control group	
1. Feeling tired/weakness	15	9	24
2. Stomach upset	4	6	10
3. Nausea/vomiting	0	7	7
4. Diarrhea	1	1	2
5. Constipation	1	6	7
6. Changes in taste or appetite	1	1	2
7. Thirst	0	1	1
8. Changes in weight	0	1	1
9. Trouble heart beating (tachycardia/bradycardia)	8	7	15
10. Symptoms during effect	0	0	0
11. Thoracic pain	3	10	13
12. Headache	3	9	12
13. Dizziness/lightheadedness	7	13	20
14. Blackout	1	4	5
15. Dry mouth/eye	1	5	6
16. Rash/itching	2	8	10
17. Flushing	0	1	1
18. Edema	4	9	13
19. Trouble breathing	5	8	13
20. Dry cough	1	7	8
21. Sexual problems	1	2	3
22. Raynaud phenomenon	1	2	3
23. Muscle cramps	4	5	9
24. Bruising	0	0	0
25. Swarming/pricking sensations	2	0	2
26. Eyesight changes	0	1	1
27. Yellow eyes or skin	0	0	0
28. Sleep disturbance	1	5	6
29. Mood swings	0	1	1
30. Others	28	26	54
All	94	155	249

Preliminary data suggest that when the selected pharmacological class of antihypertensive agent does not correspond to the patient's hemodynamic state, BP reduction is limited, BP fall is delayed, and side-effects may occur more frequently. By contrast, when the pharmacological class of antihypertensive treatment is adapted to the hemodynamic state (for instance, diuretics for hypervolemia; calcium antagonists, angiotensin converting enzyme inhibitors or a-receptor blockers for increased peripheral resistances; b-blockers for hyperinotropy), BP reduction occurs more rapidly and to a greater extent (Publication I; Fadl El Mula, 2016).

The value of using impedance cardiography-derived hemodynamic data as an adjunct to therapeutic decision-making in the treatment of hypertension has been supported in a meta-analysis, which demonstrated that impedance cardiography-based approaches are in keeping with previously advocated strategies which incorporate patient-individualized drug regimens, evidence-based medicine, and practical, easy to apply, cost-effective principles to further improve hypertension control rates (Ferrario et al., 2010).

Our findings show that there were fewer adverse events in the IHM than in the control group. Though most adverse events were of the more general type and not necessarily related to drug treatment for hypertension (Table 4), our data suggest that matching drug choice with the individual hemodynamic profile is likely to have favoured an overall reduction in side-effects, and thus made treatment more acceptable (Publication II).

This result may also suggest that choice of antihypertensive treatment based on patient's hemodynamic profile may lead to administration of more acceptable and better tolerated drugs, which may favour patient's compliance, and in the end, improve hypertension control. Along the same line we find it interesting that IHM-based approach led to a significantly different choice of antihypertensive drugs during follow-up as compared with controls, in particularly to a higher use of diuretics and lower use of b-blockers, with no significant differences in the prescription of other drug classes. We may speculate that such changes in medication may be related to the concomitant finding of less unspecific adverse events.

At 6 months, fractions of patients using diuretics were 41 (52%) vs. 65 (84%), respectively, in the control and the intervention group, which probably enhanced the likelihood of showing a difference in BP between groups. Diuretics comprised 13% of all the drugs used, but the number of patients taking at least one diuretic increased from 35 of 79 (44% at baseline) to 41 of 79 (52% at visit 6) in control group, and from 26 of 77 (34%) to 65 of 77 (84%) in the IHM group (Publication II).

It is an interesting point to note that the use of diuretic was limited to 52% of patients in the control group whereas the ESH guidelines recommend diuretic in most drug combinations. We have no further detailed explanation for this finding except that this is 'clinical practice' even in ESH hypertension specialist centers, and that the drug choice was based on assessment of individual clinical profile also in the control group.

This could be driven by convention that the purpose of the hypertension treatment is lowering the blood pressure, and as all the recognized groups of hypertension drugs do it, adding the diuretics is considered unnecessary despite the requirement in the EHS treatment protocols. Treatment should be geared towards selecting the best combination that improves drug compliance and decreases negative side effects.

5.3 Noninvasive hemodynamic monitoring as a guide to drug treatment of uncontrolled hypertensive patients: effects on home blood pressure in the BEAUTY study (Publication III)

The aim of the present study was to explore whether the IHM-approach improves the blood pressure control based on home BP measurements, and test the hypothesis that treatment effect may be better visualized in the home BP changes (Publication III). Recently, the usefulness of self-measured BP at home (home BP measurement) for the management of hypertension has been reported in many studies. When compared with office BP, home BP yields multiple measurements over several days taken in the individual's usual environment and is more widely available (Mancia, 2013; Kikuya et al., 2008).

A large systematic review has demonstrated that home BP is a significant predictor of cardiovascular mortality and cardiovascular events and an important prognostic variable over and above that of office BP (Ward et al., 2012).

Primary objective of the study was to explore whether monitoring hemodynamic parameters and applying a predefined algorithm of drug selection (i.e. IHM) with the Hotman® System improves the control of daytime SBP at ambulatory blood pressure monitoring (ABPM), as compared to standard drug selection (i.e. without IHM) during a 6-month intensive treatment program. One of the secondary objectives was to explore whether IHM improves the blood pressure control according to home BP measurements, which was the focus of the Publication 3 (Publication III).

Patients aged 18–85 years of either gender were referred from general practices responding to letters of invitation or were recruited directly by newspaper advertisements or referrals to the university outpatient clinics. They were worked-up at the five participating university hospitals in the time period from January 2011 through December 2012 by experienced physicians. Of the 315 screened patients 167 met the inclusion criteria and were randomized into two groups, with outcome available for 156 patients. Among these 156 patients, 84 (54%) entered into the sub-study that included additional home blood pressure measure (HBPM). This subgroup was not significantly different from the subgroup without HBPM.

Home BP was available for 46 IHM and 38 control group patients at the beginning of the study and at 6 months. Home BP was measured for one week before each study visit. Home SBP and DBP were determined as the average of all remaining morning and evening values for the period considered. The effects of each management strategy were assessed by comparing the home BP values obtained in two scheduled occasions, i.e. before the randomization visit and before the last visit (Publication III).

The baseline characteristics of 84 UCH patients randomized to IHM adjusted drug treatment (n = 46) and to classical clinical adjustment of medical treatment (n = 38) are presented in Table 5 (Publication III).

Table 5. Demographics of subjects who had home BP at both Visit2 and Visit6 (Publication III).

HOME BP measurement:		Yes			No	*P*-value of χ^2 comparing pts with and without HOME BP
		Total N pts	IHM group N (Percentage, %)	Control group N (Percentage, %)	Total N pts	
All		84	46(100)	38(100)	72	
No. of subjects by Center	France	1		1(3)	2	<0.001[a]
	Italy	10	6(13)	4(11)	9	
	Poland	24	12(26)	12(31)	10	
	Estonia	49	28(61)	21(55)	1	
	Norway	0			50	
Sex	Male	45	24(52)	21(55)	48	0.0966
	Female	39	22(48)	17(45)	24	
BMI continuous, kg/m2	Mean (standard deviation)	30(4)	30(4)	30(4)	29(4)	0.1632[b]
BMI categorical	≤24.9	13	6(13)	7(18)	14	0.1661
	25–29.9	28	20(44)	8(21)	32	
	≥30	43	20(44)	23(61)	26	
Race	Caucasian	84	46(100)	38(100)	69	a 0.0961
	Black	0			3	
Smoking habits	0 (non-smoker)	78	44(96)	34(90)	62	0.3243
	1–3	1	1(2)	–	3	
	≥4	5	1(2)	4(11)	7	
Alcohol habits	0 (teetotal)	8	4(9)	4(11)	9	0.3469a
	occasional	69	38(83)	31(82)	52	
	1 drink/day	3	2(4)	1(3)	7	
	2 drinks/day	4	2(4)	2(5)	3	
	>2 drinks/day	0			1	
No. of antihypertensive agents at baseline (Visit 2)	Mean (standard deviation)	3.2(1.1)	3.0(1.0)	3.4(1.1)	3.2(1.0)	0.7491b

[a]Fisher exact test.
[b]t-test.
Note: data are expressed as number (percentage) for categorical variables and mean (standard deviation) for continuous variables.

Home blood pressure changes between study end, baseline and control rates at study end, are demonstrated in Table 6 (Publication III).

Home BP displayed at 6 months a significantly greater reduction in IHM (–21.1 ± 17.7 mmHg) than in controls (–10.2 ±13.0 mmHg, P = 0.002). Home SBP changed from 152.1 ±15.8 and 149.8 ±11.8 mmHg to 131.0 ±11.1 and 139.6 ±12.8 mm Hg in IHM group and control group, respectively, showing significantly greater reduction in IHM than in control group (d = –10.9 mmHg, 95% CI –17.77, –4.02, p = 0.002, Table 6), which remained significant after multiple adjustment particularly for baseline home SBP, recruiting center, age, sex and BMI (SBP IHM-Control = –9.63 mmHg, 95% CI = –14.28, –5.11, $p < 0.0001$). Figure 6 demonstrates results of ABPM and HBPM at the beginning and at the end of the study in the IHM group compared to the control group (Publication III).

Table 6. Home blood pressure values and control rates at 6 months (Publication III).

Changes in HMBP (visit 6-visit 2)	IHM group (N = 46) Mean (SD)	Control group (N = 38) Mean (SD)	Diff (IHM-Control) Mean (95% CI)	*P*-value
Home SBP	−21.1 (17.7)	−10.2 (13.0)	−10.90 (−17.77, −4.02)	0.002
Home DBP	−7.6 (9.0)	−6.9 (10.6)	−0.67 (−4.91, 3.58)	0.756
SBP and DBP normalization at 6 months	*n (%)*	*n (%)*		
Home SBP(<135 mm Hg)	30 (65%)	12 (32%)		0.002
Home DBP(<80 mmHg)	34 (74%)	27 (71%)		0.770

The key finding of the present study is a statistically significant difference in reduction of home BP between groups (Publication III).

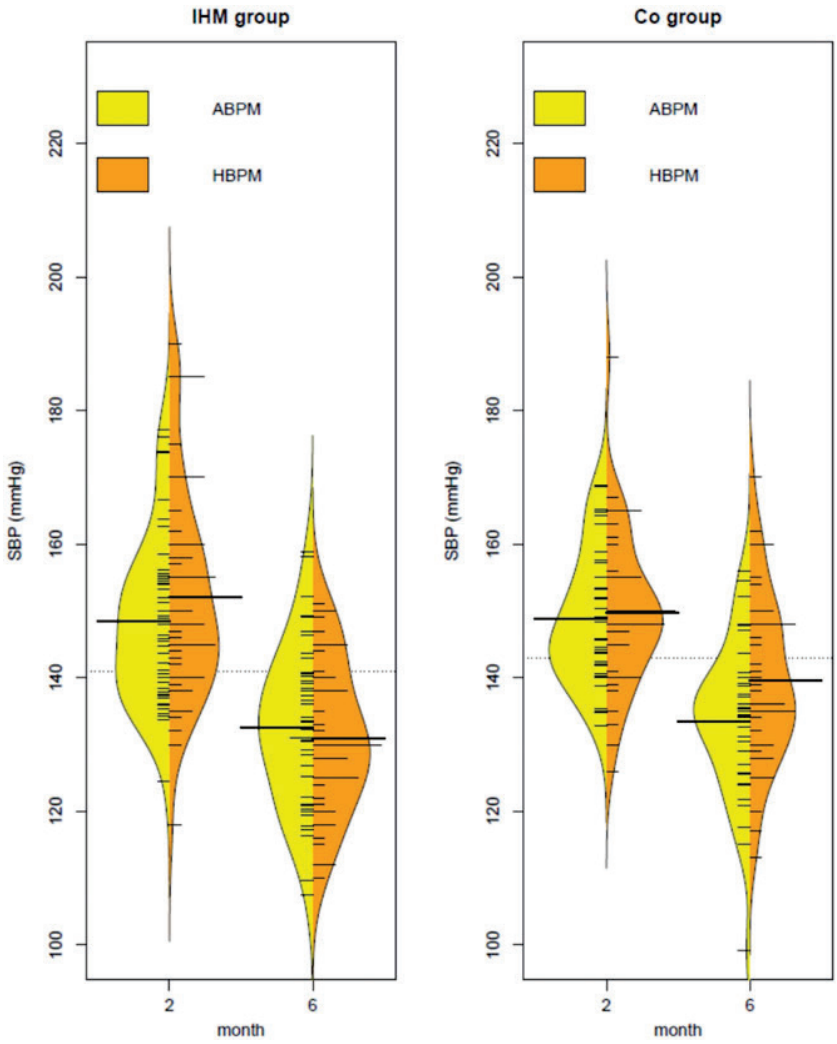

Fig 6. Comparison of home and ambulatory BP in the two groups. (Publication III).

The advantages of home BP monitoring in the management of treated hypertensive patients have been reported in many studies (Publication III; Obara et al., 2010; Márquez-Contreras et al., 2006). During the last years, guidelines have placed much greater emphasis on the utilization of out-of-office measurements including home BP measurements (Publication III; Mancia et al., 2013; Leung et al., 2016). Home BP measurement has been demonstrated to be concordant with ambulatory blood pressure monitoring. Home BP values are obtained under stable conditions and can eliminate the white coat effect (Publication III; Imai et al., 2001).

Our findings are in line with the evidence supporting the use of out-of-office monitoring in all aspects of routine clinical care, which has increased substantially in recent years and is reflected in an increased utilization of home BP monitoring by patients and clinicians (Sheppard et al., 2016). Home BP self-measurement and monitoring improves patient's

awareness and their adherence to prescribed treatment, thus favouring a better management of hypertension. This represents an important complementary support to the doctor-patient relationship in the office, with a high potential for improving hypertension management (Publication III; Lee et al., 2016; Obara et al., 2010).

The main finding of the present study is that home BP displayed at 6 months had a significantly greater reduction in IHM than in controls, whereas office did not. This emphasizes the superiority of HBPM over office BP measurements in detecting different BP effects induced by different management strategies (Publication III).

Psychology plays an important role in blood pressure regulation in clinical practice. Especially important is this when measuring blood pressure in doctor's office, where we often get too high values because of the "white coat syndrome", which in turn tends to lead to over treatment.

On the other hand, it is important to consider abundance of stressful situations in everyday life, such as pressures at work or in being in traffic. The elevated blood pressure might be caused by the high levels of stress hormone in bloodstream.

In most occasions, person is normally calm and resting in home situation, and the blood vessels are also relaxed, which is an important mechanism in regulation of blood pressure. Blood vessels dilate and blood pressure lowers.

This way, the results measured in two different situations: 1) in doctors' office (office BP), which simulates stressful situations, and 2) at home (home BP), which simulates resting gives us more diverse information than considering only one of these measurements.

Based on these factors, home measurements could be very important when we evaluate the efficiency of the treatment. Importantly, we assume that the blood pressure device is decent and the patient is properly instructed and follows the best practice.

In our opinion, the blood pressure measurement results at home are undervalued in clinical practice. Home measurements combined with adequate measuring techniques during extended periods help us to evaluate patient's blood vessels' condition, and as such, make our treatment decisions more balanced.

These specific features of the home BP measurements could make it the best BP assessment method for drug trials and intervention studies. Home BP is more similar to «basal» blood pressure. Our data shows that home BP is more sensitive to drug selection algorithm in response to noninvasive hemodynamic monitoring than office and ABPM in patients with uncontrolled hypertension (Publication III).

Study limitations

We have to acknowledge a few limitations of our study.
First, we had limited sample size - the number of patients was relatively low.

Second, situations where the same doctor was responsible for the treatment of patients in both arms might have carried a potential bias. In principle, the lead investigators were blinded for the IHM readings in patients in the control arm. Fadl El Mula (2016) has indicated that it is still possible to presume that information may have leaked to physician, either from technician or patient.

Third, home BP monitoring was performed in four study centres out of five and not in all BEAUTY study patients as home BP being a secondary endpoint and thus not obligatory according to the study protocol.

However, in spite of these limitations, we have found a statistically significant greater reduction in home systolic blood pressure using IHM than in the control group (Publication III).

6 CONCLUSIONS

The main results of the thesis are as follows:

1. Hemodynamic measurements show that almost all patients presented at least one altered hemodynamic modulator: intravascular hypervolemia (96.4%) and/or hypoinotropy (42.5%) and/or vasoconstriction (49.3%). Eleven combinations of hemodynamic modulators were present in the study population, the most common being concomitant hypervolemia, hypoinotropy and vasoconstriction in 51 (38%) patients. Altogether, six different hemodynamic states (pairs of mean arterial pressure and stroke index) were found (Publication I).

2. Noninvasive hemodynamic monitoring associated with a drug selection algorithm induced similar reductions in ambulatory daytime and office systolic blood pressure compared with conventional drug selection in uncontrolled hypertensive patients referred to the European Hypertension Excellence Centers (Publication III).

3. Average number of adverse events was significantly lower in integrated hemodynamic management than in control group. The incidence rate ratio was 0.63 for total adverse events and 0.62 for drug-related adverse events (Publication II).

4. Drug selection algorithm based on noninvasive hemodynamic monitoring induced larger reduction in home blood pressure compared to conventional drug selection in uncontrolled hypertensive patients (Publication III).

Finally, the results of this doctoral study suggest that the integrated hemodynamic monitoring is useful in patients with uncontrolled hypertension by reducing side-effects (Publication I). This result also suggests that choice of antihypertensive treatment based on patient's hemodynamic profile may lead to administration of more acceptable and better tolerated drugs, which may favour patients' compliance and, in the end, improve hypertension control.

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Abstract

Noninvasive Hemodynamic Monitoring as a Guide to Drug Treatment of Uncontrolled Hypertensive Patients

Problem: Uncontrolled hypertension (UCH) often leads to early onset of serious complications and deaths. The most common cause of UCH is inadequate or suboptimal pharmacological treatment, often caused by selection of antihypertensive drugs without consideration to hemodynamic status (volemia, peripheral resistance, cardiac inotropy, heart rate). When the pharmacological class of antihypertensive treatment is adapted to the hemodynamic state (e.g., diuretics for hypervolemia, calcium-channel blocker/ACE inhibitor/ angiotensin receptor blockers for increased peripheral resistance), blood pressure reduction may occur more rapidly and to a greater extent.

Aims: The thesis had four aims: a) to assess the treatment efficacy of UCH using noninvasive monitoring of hemodynamic parameters and impedance-cardiography-guided (ICG) therapy; b) to evaluate hemodynamic modulators and subsequent hemodynamic status in patients with UCH; c) to investigate whether utilizing noninvasive monitoring of hemodynamic parameters combined with a drug selection algorithm (integrated hemodynamic management – IHM) improves UCH and reduces side effects compared to the conventional drug selection; and d) whether the IHM may improve blood pressure control based on home BP measurements.

Method: The data comes from a clinical evaluation conducted in five European Hypertension Excellence Centers. This multicenter prospective randomized open end-point (PROBE) parallel group design study compared the reduction of daytime SBP- ABPM over 6 months in 2 groups: the IHM group received impedance-cardiography-guided therapy, and co-group was provided with standard antihypertensive care (ESH, 2007).

Patients aged 18–85 years of either gender were referred to the university outpatient clinics from general practices. The final sample included 167 patients with UHT who had been treated with at least two antihypertensive drugs. Home BP was available for 46 IHM and 38 control group patients at the baseline and at 6 months, and was measured one week before ambulatory visit.

The hemodynamic status and modulators were assessed noninvasively with the HOTMAN® System. Thoracic electrical bioimpedance (TEB) measurement was obtained as a part of routine care.

Results: We identified six different hemodynamic states. Almost all patients (98.5%) presented at least one altered hemodynamic modulator: intravascular hypervolemia was present in 96.4% of patients, and/or hypoinotropy in 42.5%, and/or vasoconstriction in 49.3% of cases.

Mean office systolic blood pressure decreased in both the integrated hemodynamic management and the control group. No statistically significant difference was found between the groups in ambulatory blood pressure monitoring and office blood pressure changes at 6 months. However, the integrated-hemodynamic-management-group patients displayed a significantly greater reduction in home blood pressure at 6 months (Publication III).

Safety analysis included 80 and 81 patients from integrated hemodynamic management and control group, respectively. Average number of adverse events was significantly lower in the integrated hemodynamic management than in control group.

The integrated -hemodynamic- management-based approach led to changes in choice of antihypertensive drugs at the follow-up, particularly to a higher use of diuretics and lower use of betablockers. We hypothesize that such changes in medication may be related to the concomitant finding of fewer unspecific adverse events.

At 6 months, fractions of patients using diuretics were 41 (52%) vs. 65 (84%), respectively, in the control and the intervention group, which probably enhanced the likelihood of showing a difference in blood pressure between groups. It is an interesting point to note that the use of diuretic was limited to 52% of patients in the control group whereas the ESH guidelines recommend diuretic in most drug combinations in treatment of uncontrolled hypertension.

Conclusions: Results of this doctoral theses suggest that treatment changes made on the basis of results of hemodynamic monitoring reduce home blood pressure and side-effects in patients with uncontrolled hypertension. We conclude that home blood pressure is more sensitive to drug selection algorithm based on noninvasive hemodynamic monitoring than office blood pressure and ambulatory blood pressure monitoring in patients with uncontrolled hypertension. The results suggest that choice of antihypertensive treatment based on patient's hemodynamic profile was associated with overall reduction of adverse side effects, and it may lead to administration of better tolerated drugs, which may favour patients' compliance and, in the end, improve blood pressure control.

Lühikokkuvõte

Hemodünaamika hindamine impedantskardiograafia meetodil ja ravimresistentse hüpertooniatõvega patsientide ravitulemuse parandamine täpsema ravimivalikuga

Probleem: Ravimresistentne hüpertooniatõbi (HT) viib sageli varaste tüsistuste avaldumiseni ja enneaegse surmani. Kõige levinum ravile allumatu HT põhjus on ebaadekvaatne või suboptimaalne farmakoloogiline ravi, mille põhjuseks on patsiendi hemodünaamikat (voleemia, perifeerne resistentsus, kardiaalne inotroopia, frekvents) mittearvestav ravimivalik. Kui HT ravi ravimiklass on kohandatud patsiendi hemodünaamilisele seisundile (st diureetikum hüpervoleemia ja kaltsiumkanali blokaator/ angiotensiini konverteeriva ensüümi inhibiitor/ angiotensiiniretseptori blokaator perifeerse resistentsuse korral), siis võib olla vererõhu langus kiirem ja ulatuslikum.

Eesmärgid: Doktoritööl on neli eesmärki: a) hinnata ravimresistentse HT-ga patsientide hemodünaamika parameetreid ja ravitulemuse paranemist mitteinvasiivse impedantskardiograafia (IKG) -juhitud täpsema ravimivalikuga b) hinnata ravimresistentse HT-ga patsientide hemodünaamilisi modulaatoreid ja hemodünaamilist staatust c) hinnata, kas hemodünaamiliste parameetrite mitteinvasiivne monitoorimine kombineerituna ravimivaliku algoritmiga (IHM-integrated hemodynamic management) parandab ravimresistentset HT ja vähendab ravi kõrvaltoimeid võrreldes tavalise ravimivalikuga ja d) kas IHM parandab HT ravitulemusi kodumõõtmiste alusel.

Meetod: Viies Euroopa Hüpertensiooni Ekstsellentsikeskuses tehtud multitsentrilises prospektiivses randomiseeritud PROBE disainiga paralleelgruppide uuringus võrreldi päevase süstoolse ja ambulatoorselt mõõdetud vererõhu muutuseid 6 kuu jooksul kahel grupil: IHM grupp sai IKG-juhitud ravi, kontrollgrupp sai tavaravi, vastavalt ESH/ESC 2013 juhistele.

Mõlemast soost patsiendid vanuses 18-85 aastat olid suunatud ülikoolikliinikutesse. Uuringusse kaasati 167 ravile allumatu HT-ga patsienti, keda oli varem ravitud vähemalt kahe HT ravimi kombinatsiooniga. Kodumõõtmised, mis olid sooritatud ühe nädala jooksul enne ambulatoorset visiiti nii uuringu 2. kui ka 6-ndal kuul olid kasutatavad 46 IHM ja 38 kontrollgrupi patsiendil.

Hemodünaamilist seisundit ja modulaatoreid hinnati igal visiidil mitteinvasiivselt HOTMAN® süsteemiga rindkere elektrilise bioimpedantsi meetodil.

Tulemused: On määratletud kuus erinevat hemodünaamilist seisundit. Enamikel patsientidest (98,5%) esines vähemalt üks muutunud hemodünaamika modulaator: intravaskulaarne hüpervoleemia esines 96,4% patsientidest, ja/või hüpoinotroopia 42,5% ja/või vasokonstriktsioon 49,3% juhtudest. Keskmine süstoolne visiidirõhk langes nii IHM kui ka kontrollgrupis. Statistilist erinevust ambulatoorse ja visiidirõhu languses kuuendal kuul ei esinenud. Siiski langes kodumõõtmistel saadud vererõhuväärtus kuuendaks kuuks olulisel määral (Publication III).

Kõrvaltoimete analüüs haaras 80 patsienti IHM grupist ja 81 patsienti kontrollgrupist. Kõrvaltoimete keskmine esinemissagedus oli IHM grupis oluliselt madalam kui kontrollgrupis.

Mitteinvasiivse IKG-põhine lähenemine muutis HT ravimivalikut, ennekõike suurendades diureetikumide ja vähendades beetablokaatorite kasutamist. Minu hüpotees on, et need erinevused ravimite valikus võivad olla vähemate kõrvaltoimete esinemissageduse põhjuseks.

Kuuendal kuul oli diureetikumide kasutajate hulk 41 (52%) kontrollgrupis ja 65 (84%) IHM grupis, mis tõenäoliselt suurendas vererõhuerinevuste esinemise tõenäosust gruppide vahel. On huvitav märkida, et diureetikume said ainult 52% kontrollgrupi patsientidest kuigi ESH ravijuhised soovitavad diureetikume kasutada enamikes ravile allumatu HT ravimikombinatsioonides.

Järeldused: Doktoritöö tulemused kinnitavad, et ravile allumatu hüpertooniatõve patsientide hemodünaamika monitoorimine ja impedantskardiograafia-juhitud ravimivalik vähendavad kodumõõtmiste vererõhuväärtuseid ja ravi kõrvaltoimete esinemissagedust. Järeldan, et ravile allumatu hüpertooniatõvega patsientide kodumõõtmiste tulemused on viisidi- ja ambulatoorse vererõhu väärtustest tundlikumad mitteinvasiivse hemodünaamika monitoorimisele ja impedantskardiograafia-juhitud ravimivalikule. Tulemused lubavad oletada, et hüpertooniatõve ravimivalik, mis põhineb patsiendi hemodünaamilise profiilil, on seotud kõrvaltoimete esinemissageduse üldise langusega ja võib viia paremini talutavate ravimite kasutamiseni, mis võib omakorda parandada patsientide ravisoostumust ning parandada hüpertooniatõve ravitulemusi.

Appendix

Publication I

M. Viigimaa, **A. Talvik**, W. Wojciechowska, K. Kawecka-Jaszcz, I. Toft, G. S. Stergiou, E. G. Nasothimiou, V. Kotsis, E. Agabiti Rosei, M. Salvetti, M. Dorobantu, N. Martell-Claros, M. Abad-Cardiel, R. Hernàndez-Hernàndez, M. Doménech & A. Coca. Identification of the hemodynamic modulators and hemodynamic status in uncontrolled hypertensive patients. Blood Press. 2013; 22:362–370.

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ORIGINAL ARTICLE

Identification of the hemodynamic modulators and hemodynamic status in uncontrolled hypertensive patients

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Abstract

Only 20–30% out of the treated hypertensive patients in Europe are achieving blood pressure (BP) control. Among other recognized factors, these poor results could be attributable to the fact that for many doctors it is very difficult to detect which is the predominant hemodynamic cause of the hypertension (hypervolemia, hyperinotropy or vasoconstriction). The aim of the study was to use non-invasive thoracic electrical bioimpedance (TEB) to evaluate hemodynamic modulators and subsequent hemodynamic status in uncontrolled hypertensive patients, receiving at least two antihypertensive drugs. A number of 134 uncontrolled hypertensive patients with essential hypertension were evaluated in nine European Hypertension Excellence centers by means of TEB (the HOTMAN® System). Baseline office systolic and diastolic BP averaged 156/92 mmHg. Hemodynamic measurements show that almost all patients (98.5%) presented at least one altered hemodynamic modulator: intravascular hypervolemia (96.4%) and/or hypoinotropy (42.5%) and/or vasoconstriction (49.3%). Eleven combinations of hemodynamic modulators were present in the study population, the most common being concomitant hypervolemia, hypoinotropy and vasoconstriction in 51(38%) patients. Six different hemodynamic states (pairs of mean arterial pressure and stroke index) were found. Data suggest that there is a strong relation between hypertension and abnormal hemodynamic modulators. This method might be helpful for treatment individualization of hypertensive patients.

Key Words: *Hemodynamic modulator, hypertension, non-invasive thoracic electrical bioimpedance*

Introduction

Despite the clear benefits of numerous classes of antihypertensive therapy, hypertension remains poorly controlled in clinical practice and blood pressure (BP) control of hypertensive patients remains a major unsolved problem in Europe (1,2). This has significant implications for public health, because low BP control has been shown to be associated with a marked increase in the risk of fatal and non-fatal cardiovascular (CV) events (3,4). Antihypertensive agents reduce morbidity and mortality associated with hypertension through BP control. Studies have indicated that even small reductions in systolic or diastolic BP result in 30% and 40% reductions in the risk of ischemic heart disease and fatal stroke, respectively (5).

According to current recommendation, five major classes of antihypertensive agents [thiazide diuretics, calcium antagonists, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor antagonists

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and beta-blockers] are suitable for the initiation and maintenance of antihypertensive treatment, alone or in combination (6). Choice of antihypertensive drugs is made considering previous experience with the drug, effect of drugs on CV risk factors, presence of specific disease or disorders, and drug cost, among others. The reasons why hypertension is poorly controlled include inadequate or suboptimal antihypertensive medication, medication intolerance, patient non-compliance, underestimation of comorbidities, physician perceptions about drug effectiveness, medication cost, etc. All guidelines for the management of hypertension emphasize the need to improve long-term CV outcomes as well as to increase the proportion of patients achieving target BP (6), without providing a specific algorithm.

Hypertension is a multifactorial disease, but the hemodynamic component of BP physiology includes factors that affect intravascular volume, cardiac inotropy and systemic vascular resistance. Usually, physicians do not have the possibility of evaluating the hemodynamic causes of the hypertension – hypervolemia, hyperinotropy or vasoconstriction – or whether there is a combination of these causes. For this reason, the BP problem is treated like a symptom, without paying attention to the hemodynamic causes of BP elevation, and the selection of antihypertensive agents is often done independently of the hemodynamic status of the patient. When the pharmacological class of antihypertensive agent does not correspond to the hemodynamic state, BP reduction is limited. By contrast, when the pharmacological class of antihypertensive treatment is adapted to the hemodynamic state [for instance diuretics for hypervolemia, or calcium-channel blocker/ACE inhibitor/angiotensin receptor blockers (CCB/ACEI/ARB) for increased peripheral resistances], BP reduction may occur more rapidly and to a greater extent (7–10).

The study purpose was to assess hemodynamic modulators (intravascular volemia, inotropy and vasoactivity) and hemodynamic status [mean arterial pressure (MAP) and stroke index (SI)] in uncontrolled hypertensive patients using a non-invasive thoracic electrical bioimpedance (TEB) technique (the HOTMAN System®, Hemo Sapiens Inc.) and possible relationship between uncontrolled hypertension and untargeted hemodynamic modulators.

Materials and methods

A clinical evaluation was conducted in nine European Hypertension Excellence Centers over a period of 2 months, using a common standardized procedure. Centers included 134 uncontrolled hypertensive patients with essential hypertension treated with at least two antihypertensive drugs. According to the protocol, any patient meeting inclusion and exclusion criteria attended each Center of Hypertension over the study period was chosen to be evaluated. All patients were already following an antihypertensive treatment, but were not controlled under the previous medication (BP values $>140/90$ mmHg clinically and $>130/80$ mmHg average of 24 h on ambulatory BP monitoring). Office BP was taken in concordance with "2007 ESH Guidelines for the management of arterial hypertension", with the patient seated using an oscillometric method.

We implemented the HOTMAN® System (Hemo Sapiens Inc.), a computer operating device based on TEB for providing non-invasive assessment of hemodynamic modulators and evaluation of the hemodynamic status of the patients. TEB measurement was obtained as a part of routine care. Hemodynamic parameters were achieved in supine patients after 10 min of rest. The TEB technique belongs to impedance cardiography (ICG), a non-invasive hemodynamic diagnostic and monitoring technology. ICG has demonstrated its usefulness and reproducibility in various populations (11–14).

The principle of TEB is based on measuring the thorax impedance (resistance of body tissues) when is applied an alternating current with a very low intensity and high frequency. The measurement current passes between two pairs of TEB sensors located on the upper neck and upper abdomen in a direction parallel to the spine. Four other receptor sensors are located at the root of the neck and at the diaphragm level. These sensors detect ECG signals as well as the voltage of the electrical current that crosses the thorax, which is proportional to the thoracic impedance (15). HOTMAN System functioning is based on a proprietary very low TEB technology, utilizing very low TEB measurement current with fully digitized, high sampling rate generation and acquisition of the TEB signal. The TEB measurement current is only 7 μA, safe for the patients and with high reproducibility. Its digital data processing results in wide bandwidth, high-quality and high-resolution TEB signal, unavailable with analogue acquisition methodologies.

These features enable precise measurements of TEB signal's key magnitude and timing events. Following the digital process of TEB and ECG signal, this technique provides information about the value of blood flow [cardiac index (CI) and SI, heart rate (HR)], contractility and left ventricle performance [ejection phase contractility index (EPCI), inotropic state index (ISI) and left stroke work index (LSWI)] and afterload [stroke systemic vascular resistance index (SSVRI), and thoracic fluid conductivity (TFC)].

Compared with the classical ICG technique, the HOTMAN® System has some different characteristics: it measures systemic vascular resistance per beat as SSVRI, a parameter not detected by other bioimpedance devices; it is the only system that offers a beat-to-beat evaluation of cardiac inotropy (ISI); and

intravascular volume is not evaluated through TFC, but calculated as a component of total contractility according to the Frank–Sterling Law. In addition, the HOTMAN® System presents the hemodynamic status of the patient and the situation of the hemodynamic modulators: volemia, inotropy, vasoactivity and chronotropy (16).

Statistical analysis

For every patient, the percent deviations of the hemodynamic modulators from its ideal values were calculated. Data were recorded in a computer database using Excel software from the HOTMAN System's printed status report.

Results

One hundred and thirty-four patients with essential hypertension were evaluated. All subjects followed antihypertensive therapy for more than 2 months and presented documented history of uncontrolled BP. During the study, office systolic and diastolic BP averaged 156/91.9 mmHg; 110 subjects (82.1%) had BP level above normal values and 24 (17.9%) patients exhibited normal BP. None of the patients with normal BP value had this value $<120/80$ mmHg. BP during hemodynamic measurements and hemodynamic parameter in study group are presented in Table I. No demographic data were collected during the study.

Patients included in the study took an average of 3.06 ± 1 antihypertensive medications belonging to five major classes of antihypertensive agents recommended by 2007 ESH/ESC Guidelines – thiazide diuretics, calcium antagonists, ACE inhibitors, angiotensin receptor antagonists and beta-blockers – alone or in combination. Only 11 (8.1%) patients were treated with centrally acting agents and six (2.2%) patients treated with six antihypertensive medications. The vast majority of patients received two or three antihypertensive drugs – 46 (34.3%) and 48 (35.8%), respectively – followed by a four-drug regimen – 29 (21.7%) (Figure 1).

Table I. Blood pressure and hemodynamic parameters in the study group.

Number of participants	134
Systolic blood pressure, mmHg	156.0 ± 21.7
Diastolic blood pressure, mmHg	91.9 ± 13.0
Mean blood pressure, mmHg	113.3 ± 14.0
Cardiac index, l/min/m^2	3.4 ± 1.5
Stroke index, ml/beat/m^2	49.6 ± 19.9
ISI, sec^{-2}	0.99 ± 0.36
LSWI, g.m/m^2	74.5 ± 28.9
SSVRI, dyn.sec.cm^{-5}.m^2	217.2 ± 121

Data are mean $\pm$ SD. ISI, inotropic state index; LSWI, left stroke work index; SSVRI, stroke systemic vascular resistance index.

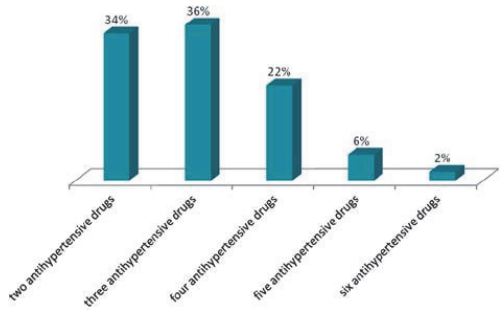

Figure 1. Numbers of antihypertensive drugs used by participants of the study.

Diuretics were the most used antihypertensive drugs and were prescribed in 71.6% of the study population. The next used antihypertensive drugs were dihydropyridine CCBs (61.9%) and ARBs (56.7%). Beta-blockers were divided in two categories – vasodilator beta-blockers and non-vasodilator beta-blockers – and they were prescribed in 24.6% and 29.8% of patients, respectively. ACE inhibitors were used in 32.8% patients and central acting drugs in 8.1%. Each antihypertensive class was split from dosage point of view in low dose, medium dose and high dose (Figure 2).

Among the whole study group, 70 (52.2%) patients were diagnosed as normodynamic (SI in normal range: 35–65 ml/m^2), 36 (26.9%) as hypodynamic (SI $<$ 35 ml/m^2) and 28 (20.9%) as hyperdynamic (SI $>$ 65 ml/m^2) (Figure 3). Hemodynamic state is defined by MAP and blood flow (SI) over one heartbeat interval. During non-invasive hemodynamic assessment, six different hemodynamic states were found: *hypertension and hypodynamic* in 30 (22.4%) patients, *hypertension and normodynamic* in 54 (40.3%) patients, *hypertension and hyperdynamic* in 18 (13.4%) patients, *normotension and hypodynamic* in six (4.5%) patients, *normotension and normodynamic* in 16 (11.9%) patients and *normotension and hyperdynamic* in 10 (7.5%) patients (Figure 3).

From these six hemodynamic states, hypertension occurred in more than 76% of patients and less than 12% reached the hemodynamic goal, being simultaneously normotension and normodynamic.

Hypertension in any individual is caused by its specific and unique contribution of abnormal levels in hemodynamic modulators. Hemodynamic measurements revealed that most of patients presented intravascular hypervolemia (96.4%), and/or hypoinotropy (42.5%) and/or vasoconstriction (49.3%).

The initial hemodynamic assessment showed the following distribution of the hemodynamic modulators (intravascular volemia, inotropy and vasoactivity), including chronotropy: hypovolemia two (1.5%) patients, normovolemia three (2.2%) patients, hypervolemia 129 (96.3%) patients, hypoinotropy 57

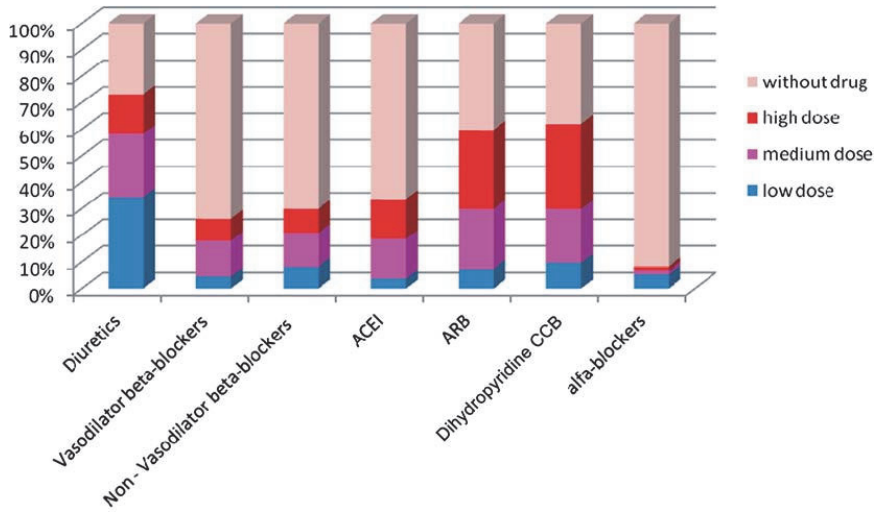

Figure 2. Antihypertensive drug usage in study group.

(42.5%) patients, normoinotropy 58 (43.3%) patients, hyperinotropy 19 (14.2%) patients, vasodilation nine (6.7%) patients, normovasoactivity 59 (44%) patients, vasoconstriction 66 (49.3%) patients, hypochronotropy 55 (41%) patients, normochronotropy 50 (37.4%) patients and hyperchronotropy 29 (21.6%) patients (Figure 4).

An abnormal hemodynamic state is a result of abnormal levels in one or a combination of hemodynamic modulators. Since any single abnormal hemodynamic modulator (intravascular volume, inotropy and vasoactivity) might be responsible for a hemodynamic disturbance, we divided the study population into four subgroups according to number of altered hemodynamic modulators: (i) all three hemodynamic modulators altered (44.8%), (ii) a combination of two altered hemodynamic modulators (22.4%), (iii) one hemodynamic modulators altered (31.3%), and (iv) no hemodynamic modulators altered (1.5%) (Figure 5).

The subgroup of patients with three altered hemodynamic modulators was the most numerous (44.8%) in the study population. This subgroup included three different combinations of altered modulators, as Figure 5 shows. In fact, the patients with concomitant *hypervolemia + hypoinotropy + vasoconstriction* represent

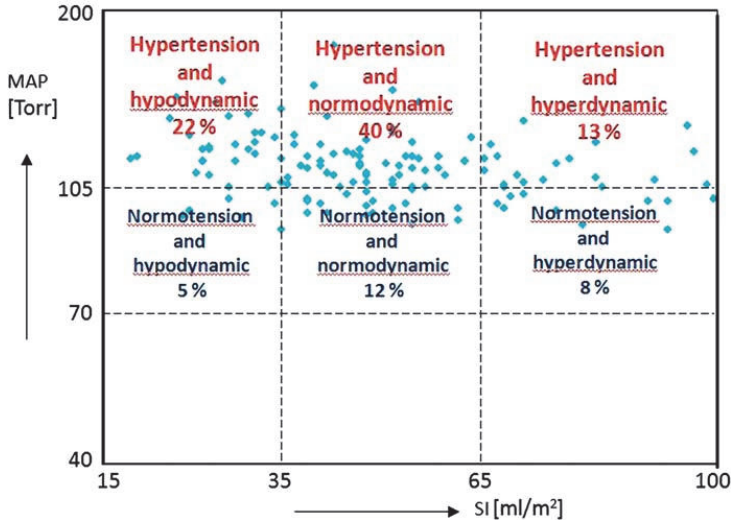

Figure 3. Scattergram of hemodynamic state of all patients measured in the study with superimposed percentage of correspondent hemodynamic states.

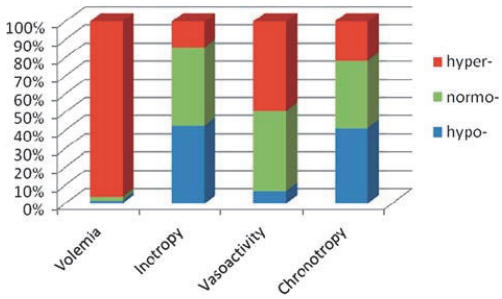

Figure 4. Hemodynamic modulators distribution.

the biggest homogenous population in the study group. Despite a similar combination of altered modulators, 34 patients in this group were hypodynamic (low SI value) and 17 patients normodynamic. Table II shows the complete hemodynamic profile and antihypertensive drug treatment in all subgroups.

A combination of two altered hemodynamic modulators was met in 30 (22.4%) patients and contains five pairs of different altered hemodynamic modulators: *hypervolemia+ vasoconstriction*, *hypervolemia+ hyperinotropy*, *hypervolemia+ hypoinotropy*, *hypervolemia+ vasodilation* and *hypovolemia+ vasoconstriction*.

Almost one third of total study patients (31.3%) belonged to the subgroup with one hemodynamic modulator altered. With one exception, this altered hemodynamic modulator was hypervolemia. Again, SI values varied broadly despite similar hemodynamic modulator altered (Table II). Only two patients exhibited normal values for all hemodynamic modulators. This is an interesting finding considering a total of 24 patients with normal BP, because the remaining 22 patients presented normal BP but abnormal hemodynamic profile.

Discussion

BP is a measurable end product of an exceedingly complex series of factors including those that control blood vessel caliber and responsiveness, those which control fluid volume within and outside the vascular bed, and those which control cardiac

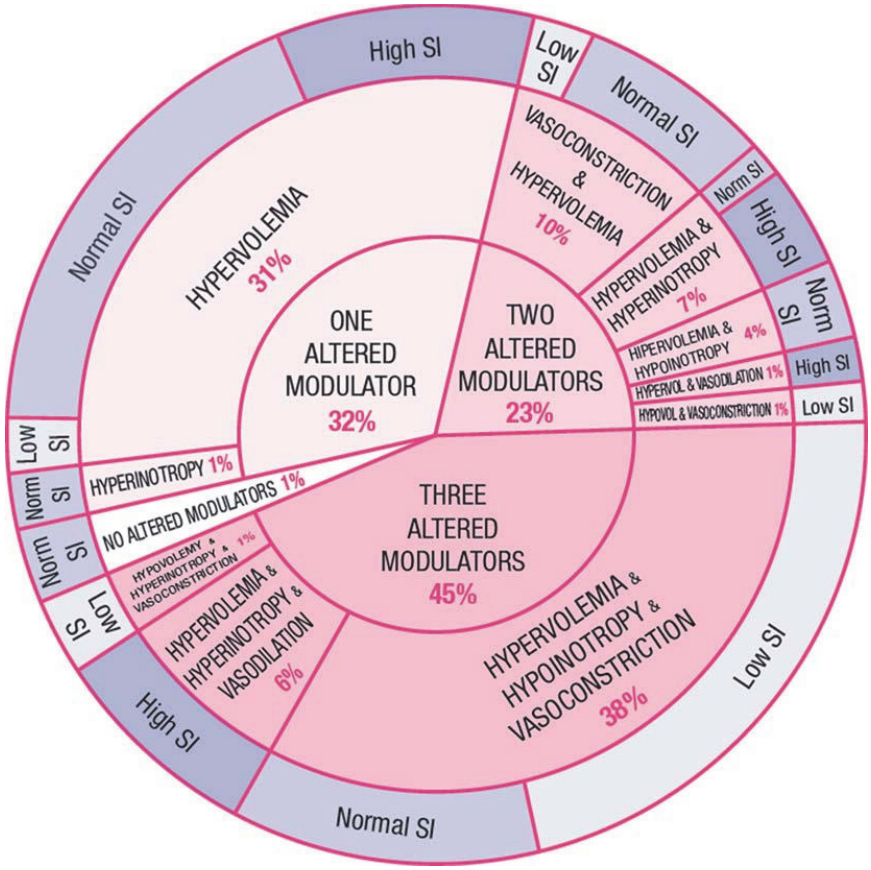

Figure 5. Subgroup distribution according to number of altered modulators.

Table II. Complete hemodynamic profile and drug distribution in each subgroup.

Subgroup of hemodynamic modulators	Number of patients	Hemodynamic modulators	Number of patients	Chronotropy (patient number and percentage in this subgroup)	Stroke Index (patient number and percentage in this subgroup)	Altered Hemodynamic modulators	Antihypertensive drugs distribution in each subgroup							
							dose of drug	Diuretic	VD-BB	N VD-BB	ACEI	ARB	CCB-DHP	α blocker
Three altered hemodynamic modulators	60 patients (44.8%)	Hypervolemy hypoinotropy vasoconstriction	51 (38%)	42 (82.4%) hypochronotropy 8 (15.7%) normochronotropy 1 (1.9%) hyperchronotropy	34 (66.7%) hypodynamic 17 (33.3%) normodynamic	Hypervolemy hypoinotropy vasoconstriction	Low	15	3	3	2	4	5	2
							Medium	20	9	7	4	15	14	1
							High	9	5	2	8	18	18	2
		Hypervolemy Hyperinotropy vasodilation	8 (6%)	8 (100%) hyperchronotropy	8 (100%) hyperdynamic	Hypervolemy Hyperinotropy vasodilation	Low	3	0	3	0	2	0	0
							Medium	0	1	2	0	0	0	0
							High	2	0	0	3	1	4	0
		hypovolemy Hyperinotropy vasoconstriction	1 (0.7%)	1(100%) hypochronotropy	1 (100%) hypodynamic	hypovolemy Hyperinotropy vasoconstriction	Low	0	0	0	0	0	0	0
							Medium	0	0	0	0	1	1	0
							High	0	0	0	0	0	0	0
Two altered hemodynamic modulators	30 patients (22.4%)	Hypervolemy normoinotropy vasoconstriction	13 (9.7%)	3 (23%) hypochronotropy 7 (54%) normochronotropy 3 (23%) hyperchronotropy	1 (8%) hypodynamic 12 (92%) normodynamic	Hypervolemy vasoconstriction	Low	6	1	2	2	0	11	1
							Medium	1	2	1	4	2	3	1
							High	2	1	1	2	2	4	0
		Hypervolemy Hyperinotropy normovasoactivity	9 (6.7%)	3 (33%) normochronotropy 6 (67%) hyperchronotropy	1 (11%) normodynamic 8 (89%) hyperdynamic	Hypervolemy Hyperinotropy	Low	2	0	1	0	0	1	0
							Medium	3	1	1	3	3	3	0
							High	2	0	1	0	1	0	0
		Hypervolemy hypoinotropy normovasoactivity	6 (4.5%)	4 (66%) hypochronotropy 1 (17%) normochronotropy 1 (17%) hyperchronotropy	6 (100%) normodynamic	Hypervolemy hypoinotropy	Low	3	0	0	0	1	0	1
							Medium	0	0	1	2	2	0	0
							High	1	2	1	0	1	3	0
		Hypervolemy normoinotropy vasodilation	1 (0.7%)	1(100%) hyperchronotropy	1 (100%) hyperdynamic	Hypervolemy vasodilation	Low	0	0	0	0	0	1	0
							Medium	0	1	0	0	0	0	0
							High	0	0	0	0	0	0	0
		hypovolemy normoinotropy vasoconstriction	1 (0.7%)	1(100%) hypochronotropy	1 (100%) hypodynamic	hypovolemy vasoconstriction	Low	0	0	0	0	0	0	0
							Medium	1	0	0	0	0	1	0
							High	0	0	0	0	1	0	0

(*Continued*)

Table II. (*Continued*)

Subgroup of hemodynamic modulators	Number of patients	Hemodynamic modulators	Number of patients	Chronotropy (patient number and percentage in this subgroup)	Stroke Index (patient number and percentage in this subgroup)	Altered Hemodynamic modulators	Antihypertensive drugs distribution in each subgroup							
							dose of drug	Diuretic	VD-BB	N VD-BB	ACEI	ARB	CCB-DHP	α blocker
One altered hemodynamic modulator	42 patients (31.3%)	Hypervolemy	41 (30.1%)	3 (7.3%)	2 (4.9%)	Hypervolemy	Low	14	2	2	1	2	5	3
		normoinotropy		hypochronotropy	hypodynamic		Medium	7	5	5	7	6	4	0
		normovasoactivity		31 (75.6%)	27 (65.9%)		High	5	3	7	6	15	14	0
				normochronotropy	normodynamic									
				7 (17.1%)	13 (31.7%)									
				hyperchronotropy	hyperdynamic									
		normovolemy	1 (0.7%)	1 (100%)	1 (100%)	hyperinotropy	Low	0	0	0	0	0	0	0
		hyperinotropy		hyperchronotropy	normodynamic		Medium	0	0	0	0	0	1	0
		normovasoactivity					High	0	0	0	0	1	0	0
No altered hemodynamic modulators	2 patients (1.5%)	normovolemy	2 (1.5%)	2 (100%)	2 (100%)	none	Low	1	0	0	0	0	1	0
		normoinotropy		normochronotropy	normodynamic		Medium	0	0	0	0	1	0	0
		normovasoactivity					High	0	0	0	1	0	0	0

VD, vasodilator; BB, beta-blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; CCB, calcium-channel blocker; DHP, dihydropyridine.

output. None of these factors is independent: they interact with each other and respond to changes in BP (17). Effective control of BP, may, potentially, be obtained from changes in lifestyle, adequate therapeutic management and compliance to treatment. The main improvements could rise from maximizing the effective use of existing therapeutic strategies and development of new approaches in hypertension management.

In numerous clinical trials, BP control is achieved in one third of patients with monotherapy, even under strict trial conditions. Different classes of antihypertensive agents, when combined, often have better antihypertensive effect than a single one due to synergistic effects and may have better tolerability when two components minimize each other's side-effects. Combination therapy is initiated when monotherapy fails, there is a high CV risk, high BP levels or subclinical organ damage is present (renal, CV damage) (6).

There are a number of likely combinations of drug therapy for hypertension from which the physician can choose, but there is no single optimal treatment for everyone with hypertension. It was noticed that the percentage of patients responsive to any drug class is limited and patients responsive to one drug are often not those responsive to another drug (6).

One major problem that should be reconsidered in the treatment of hypertensive patients is the use of drugs at the correct and most effective dosages. Another problem is that BP elevation is treated like a symptom, without paying attention to the hemodynamic causes. Physicians mainly neglect the other hemodynamic parameters like cardiac output, left ventricle contractility and vascular resistance, despite the fact that used drugs are modifying the entire hemodynamic status. This could be an explanation for the relatively low BP control rates and important associated side-effects.

The primary function of our CV system is not a generation of BP but a delivery of oxygen to all tissues. Oxygen delivery is a phenomenon related to the blood flow and not to BP. Actually, an adequate delivery of oxygen to all organs under all metabolic conditions is the true definition of CV health. In this respect, cardiac output is the ultimate expression of CV performance (18).

A healthy CV system maintains adequate supply of oxygen to all tissues under all metabolic conditions by a dynamic variation of levels of four modulators. Three of them are the systemic hemodynamic modulators (intravascular volume, inotropy and vasoactivity) and one is the perfusion flow modulator (chronotropy) (19,20). The body changes the levels of these four modulators for every heartbeat in response to a varying oxygen demand of all tissues (21).

It was proven that adequate oxygen delivery is the primary determinant in survival of high-risk,

critically ill patients (22,23). For hypertensive patients, it is much harder for clinicians to evaluate hemodynamic modulators in the absence of specific evidence. Physician perceptions and patient symptoms are examples of barriers affecting the management and control of hypertension (24). Under these conditions, it is a challenging task for the clinician to determine the optimal therapeutic combination of medications for each patient, mainly uncontrolled but compliant to hypertensive treatment. What is a correct drug and/or drug combination for one patient may be totally inappropriate therapy for another.

Regardless of the therapeutic availabilities of the last few years in the field of hypertension, at the enrollment in our study, the BP of patients who were taking at least two or more antihypertensive drugs was not well controlled. The study population shared six hemodynamic states (pairs of MAP and SI) with different needs in term of treatment in order to achieve the goal of normotension and normodynamism. This situation reflected the total contribution of actual treatment over MAP (76% still exhibiting hypertension) and SI.

Similarly to other studies involving hemodynamic assessment of hypertension (7,9,10), 96.3% of patients present hypervolemia in the absence of edema or other clinical signs of volemic overload. This can be the result of real hypervolemia but also hemodynamic compensatory effect of hypoinotropic patients, since about 40% of patient present simultaneously hypoinotropy. Anyhow, our results indicate that more intensive diuretic therapy is required in about half of the uncontrolled hypertensive patients in this study compared with the empiric selection of drugs (diuretics were used by 71.6% of patients). The issue of unidentified volume expansion is well recognized as a cause for resistance to antihypertensive therapy (25).

Also, considering the number of patients exhibiting hypoinotropy (42.5%), the dosage and/or usage of drugs with negative inotropic mechanism should be reassessed. This suggestion is furthermore sustained by the presence of 41% of patients with hypochronotropy, a possible result of the negative chronotropic effect of beta-blockers.

A significant percentage of patients (49.3%) presented increased peripheral vascular resistance. Vasoconstriction is hard to assess in current practice. These results confirm the known pathophysiology of hypertension and the association between elevated pressures and high peripheral resistance, regardless of the primary etiology. Interestingly, vasoconstriction was present despite the aggressive usage of vasodilating drugs (ACEI, ARB and dihydropyridine CCB): almost the entire population included in the study was treated with at least one vasodilating drug in different dosages – another suggestion that selection of an optimal combination of medications for the uncontrolled hypertensive patient is often empiric.

Different combinations of altered hemodynamic modulators were met in study subjects. Only two patients exhibit concomitant normal values for hemodynamic modulators. Our study provided information to confirm an important variation of hemodynamic modulators, which defined the hemodynamic profile in hypertensive patients. Comparing hemodynamic modulators in different uncontrolled hypertensive patients, a major discrepancy was noticed in term of number (from none to all abnormal hemodynamic modulators) and degree of alteration. In a prospective study, the selection of therapeutic agents based on the hemodynamic profile specific to each patient provided by TEB hemodynamic measurements led to a better control of hypertension in 84% of the studied population (10). Thoracic bioimpedance provides the clinician with reliable hemodynamic information that could only previously be obtained in the critical care unit of a hospital using a pulmonary artery catheter. Implementation of this hemodynamic information aids in identifying the hemodynamic components of hypertension, allowing the initiation and titration of medications that act more effectively.

In conclusion, our data suggest a strong relation between hypertension and abnormal hemodynamic modulators, with significant individual variation of the hemodynamic profile. Careful analysis of all hemodynamic modulators could precede pharmacological treatment modification in order to achieve a normohemodynamic status. Non-invasive hemodynamic measurements with TEB characterize hemodynamic profile and may be helpful for diagnostic and prognostic purposes, and for therapeutic decision making in hypertensive patients. The clinical benefits potentially offered by a greater use of this technique in the daily management of patients would require testing by future longitudinal outcome studies.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Publication II

FE. Fadl Elmula, P. Rebora, **A. Talvik***, S. Salerno, E. Miszkowska-Nagórna, X. Liu, M. Heinpalu-Kuum, T. Comotti, A. C. Larstorp, M. Rostrup, E. Świerblewska, M. G. Valsecchi, S. E. Kjeldsen, M. Viigimaa, K. Narkiewicz, G. Parati, S. Laurent. A randomized and controlled study of noninvasive hemodynamic monitoring as a guide to drug treatment of uncontrolled hypertensive patients. J Hypertens. 2015; 33: 2534–2545.

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Original Article

A randomized and controlled study of noninvasive hemodynamic monitoring as a guide to drug treatment of uncontrolled hypertensive patients

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Background: In the BEtter control of BP in hypertensive pAtients monitored Using the HOTMAN sYstem study, we investigated whether utilizing noninvasive monitoring of hemodynamic parameters combined with a drug selection algorithm (integrated hemodynamic management – IHM) compared with conventional drug selection may improve uncontrolled hypertension in European Hypertension Excellence centers.

Method: Uncontrolled (office SBP >140 mmHg and ambulatory daytime SBP >135 mmHg while taking ≥2 antihypertensive drugs) essential hypertensive patients were referred to five European Hypertension Excellence centers and, if eligible, were randomized to IHM-guided ($n=83$) vs. conventional (control, $n=84$) treatment adjustment in an investigator-initiated multicenter prospective randomized parallel groups controlled study.

Results: The average number of antihypertensive drugs increased from 3.1 to 4.1 in both groups and differed only in a rise of the use of diuretics in the IHM groups (from 13 to 31%). Daytime SBP, defined as the primary endpoint, decreased markedly and to the same extent from baseline to 6 months in IHM (-15.8 ± 14.8 mmHg) and control (-15.4 ± 14.5 mmHg) groups ($P=0.87$), with a similar behavior of office SBP (no between group differences, $P=0.18$). Average number of adverse events was significantly lower in IHM than in controls ($P=0.008$) but of the more general type and not necessarily related to drug treatment.

Conclusion: Thus, noninvasive hemodynamic monitoring associated with a drug selection algorithm induced similar reductions in ambulatory daytime and office SBP compared with conventional drug selection in uncontrolled hypertensive patients referred to European Hypertension Excellence centers.
Clinical Trial Registration – URL: http://www.clinicaltrials.gov. Unique identifier: NCT01482364

Keywords: ambulatory blood pressure monitoring, antihypertensive drugs, blood pressure control, integrated hemodynamic monitoring, uncontrolled hypertension

Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, blood pressure; BSA, body surface area; CI, cardiac index; GCP, good clinical practice; HR, heart rate; IRR, incidence rate ratio; ISI, inotropic state index; PWV, pulse wave velocity; SAEs, serious adverse events; SD, standard deviation; SI, stroke index; SSVRI, stroke systemic vascular resistance index; TFC, thoracic fluid conductivity

INTRODUCTION

Approximately 10–20% of patients treated for hypertension remain with uncontrolled high blood pressure (BP) despite prescription of antihypertensive drugs [1,2]. This fraction of patients is approximately 7.5% if concomitantly increased ambulatory BP (ABP) is also taken

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into account [2] and it includes patients being prescribed several antihypertensive drugs.

Drug-treated, but uncontrolled hypertension (UCH) is a worldwide problem and the mechanisms explaining UCH may be multiple. Patients may have truly severe hypertension and may need more or better selected drugs, a need frequently unmet because of physician resistance to increase or change prescriptions (physician inertia) [3]. Patients may also have secondary causes of hypertension interfering with the drug treatment, conditions usually treated by resolving the underlying problems [4]. A frequent reason for UCH is also poor drug adherence [5–7] that may often be due to side-effects induced by drugs. Side-effects, in particular, may be caused by antihypertensive drugs that have been prescribed but do not match the underlying hemodynamic cause of the high BP. Better selected treatment guided by noninvasive integrated hemodynamic management (IHM) using impedance cardiography may possibly counteract such problems and provide better BP control [8,9].

Finding people with true 'treatment resistant hypertension' is difficult [1–7]. The purpose of the present study was therefore to investigate the clinical usefulness of IHM by measuring thoracic impedance in making the choice of drugs in improving BP control in people with UCH without getting mixed up with the controversy regarding 'treatment resistant hypertension'. We used prespecified inclusion and exclusion criteria in order to include a homogenous population suitable for the aim of the study. Thus, we aimed for the first time to test this hypothesis through use of a novel device for noninvasive monitoring of hemodynamic parameters combined with a predefined algorithm of drug selection.

MATERIAL AND METHODS

Study design, objectives and patients

The BEtter control of BP in hypertensive pAtients monitored Using the hoTman sYstem study was an investigator initiated, designed and driven multicenter prospective randomized parallel groups controlled study with sites at five European Hypertension Excellence centers: Gdansk (Poland), Milan (Italy), Oslo (Norway), Paris (France) and Tallinn (Estonia) – ClinicalTrials.gov Identifier: NCT01482364. The study was overseen by a steering committee consisting of five senior investigators representing all sites (S.E.K., M.G.V., K.N., G.P., S.L.).

Primary objective was to investigate whether monitoring hemodynamic parameters and then applying a predefined algorithm of drug selection (i.e. IHM) with the hemodynamic and oxygen transport management (HOTMAN) System improves the control of daytime SBP at ABP monitoring (ABPM) in hypertensive patients, as compared with classical drug selection (i.e. without IHM) during a 6-month intensive treatment program. Secondary objectives were to explore whether IHM improves the control of SBP and DBP at ABPM, in the night and in office, and whether IHM improves patients' hemodynamic conditions and reduces the number of drug-related adverse events.

Patients aged 18–85 years of either gender were referred from general practices responding to letters of invitation or were recruited directly by newspaper advertisements or referrals to the university outpatient clinics. They were worked-up at the five participating university hospitals in the time period from October 2011 through December 2012 by physicians trained in these institutions. UCH was defined as elevated office SBP (>140 mmHg) despite regular intake of two to four or more antihypertensive drugs (towards the end of recruitment we accepted up to seven drugs but in few patients only, which is reflected by a total average of three drugs). Additionally, patients had to qualify by also having mean ambulatory daytime SBP at least 135 mmHg. Prior to the qualifying ABPM, drug treatment was unchanged for two weeks and no other change in medication was preplanned for the following 6 months. Exclusion criteria are listed in Appendix, online data supplement Table S1, http://links.lww.com/HJH/A528.

The study was approved by all relevant committees for clinical research ethics in the participating countries and by the institutional research committee of all five hospitals. All patients gave written informed consent for participation and publication of results. All patients who qualified for the procedure within the 24-month time period were included. Expenses were mostly covered by the participating hospitals and partly by grants-in-aid from one sponsor (Hemo Sapiens Inc. European Office, Bucharest, Romania), and patients were not paid.

Patients were randomized using a predetermined 2 × 2 randomization list through a website organized by the monitor of the study (Sintesi Research, Milan, Italy).

Impedance cardiography with the hemodynamic and oxygen transport management system

The IHM group had their antihypertensive medication adjusted at baseline, at 1 month and at 3 months by lead investigators in each site according to 2007 ESH/ESC hypertension guidelines and guided by using noninvasive IHM through impedance cardiography with the HOTMAN System (Hemo Sapiens Inc., San Ramon, California, USA), similarly to what was done in a previous study based on a different technology [8]. We used the management algorithm of the device. In short, this procedure aimed at tailoring the antihypertensive treatment to the underlying hemodynamic aberration such as increasing the dose of diuretic in volume overloaded patients or prescribing or increasing the dose of vasodilatory medicines in patients with high peripheral resistance, and decreasing the dose of β-blockers [or nondihydropyridine calcium-channel blockers (CCB)] in the presence of hypoinotropy [8,9]. In case of hypoinotropy, diltizem and verapamil were preferred vs. dihydropyridines if stopping β-blockers in order to maintain the same chronotopic effect. 'Chronotropism' is otherwise not included in the algorithm and was left to the discretion of the investigators. Diuretic therapy was not suspended in the event of normovolemia. The diuretic was suspended only in case of hypovolemia. Type of diuretics was not determined by protocol and physicians could choose freely among hydrochlorothiazide, bendroflumethiazide, chlorthalidone, indapamide, amiloride, furosemide, torasemide and spironactone, also in combinations and with potassium chloride in combination if indicated.

However, almost entirely thiazides were used. No study-related changes were done with statins, aspirin, allopurinol or glucose lowering drugs.

The HOTMAN system, validated against an invasive thermodilution approach [9], allows a noninvasive assessment of patient's hemodynamics with two important improvements compared with other previous similar devices: use of a very low current (7 μA, 300 – 400-fold lower than that used by other products, making it safer for the patient); and use of a new data signal processing and of an improved mathematical algorithm. Compared with classical 'impedance cardiography', which measures cardiac index (CI), stroke index (SI, i.e. stroke volume, SV/body surface area, BSA), SV, thoracic fluid content (TFC) and systemic vascular resistance index (SVRI), the HOTMAN system has some different characteristics. It measures SVRI per beat, that is, SSVRI (stroke systemic vascular resistance index), an index of vasoactivity, which is not detected by classical systems. Furthermore, the intravascular volume is not evaluated through TFC (which is subject to an overestimation bias in chronic obstructive pulmonary disease and other patients, as it is influenced by any liquid present in the thorax), but calculated as a component of total contractility according to Frank–Starling law. More specifically, intravascular volume is calculated according to the following equation: total contractility (TC) = intravascular volume (IV) + inotropy (I), so IV = TC–I (wherein TC is measured through left stroke work index) (Figs 1 and 2) [10].

Recordings by the HOTMAN System are performed with patients in the supine position, resting for 5 min before measurement and involve noninvasive measurement of thoracic impedance through placement of four pairs of thoracic electrical bio-impedance specific sensors placed on the neck and lower thorax (Fig. 1). Electrical impedance changes are digitally processed to calculate CI, SI, HR, inotropic state index (ISI), SSVRI, and IV.

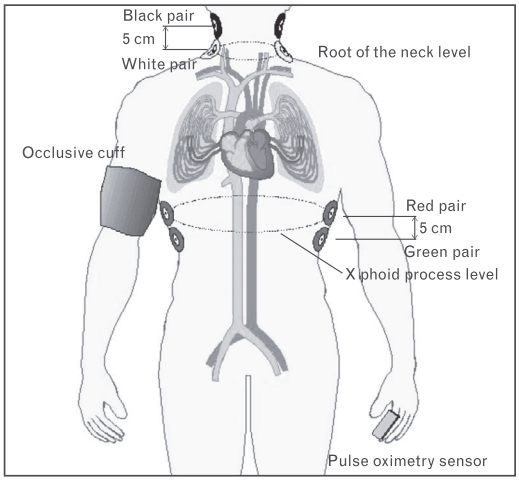

FIGURE 1 Technique for cardiac impedance measurements.

At least 3 min were required to be recorded for each patient at any occasion. If there was visible variation in the quality of signals (dZ, dZ/dt and resp) or in the hemodynamic parameters, we had to record for more minutes until we could see stable signals on the screen. Recording, later used for adjustment of treatment, was always based on at least 1 min of stable recording, so-called representative minute with the best quality of signals. Recording with incorrect and poor signals was to be considered as missing (though not accepted in the study). Hemodynamic measurements using HOTMAN system were performed also in the control group with blinding of clinician for these data. There were no significant hemodynamic differences – most importantly for (SI = inotrope) and (SSVRI = peripheral resistance) – between groups at baseline (Table S4 in the online data supplement, http://links.lww.com/HJH/A528).

The noninvasive BP acquisition is performed with an appropriate size occlusive cuff, wrapped around the arm. BP is measured by a validated oscillometric device and SBP and DBP values were entered manually into the HOTMAN computer.

Though the accuracy of HOTMAN system measurements has been previously reported through an invasive approach [9], investigation in a hospital intensive care unit is different from using the device to support treatment of hypertensive outpatients, again underlying the need for the present study. Adjustments of drug treatment, which could be done by changing either class of medication or their doses (Appendix, online data supplement Table S2, http://links.lww.com/HJH/A528), were then performed in the IHM group under the guidance of a prespecified algorithm according to patients' vascular resistance, volemia and/or inotropy (Fig. 2). Conversely the control group had their antihypertensive medication adjusted at baseline, 1 month and at 3 months by lead investigators in each site according to 2007 ESH/ESC hypertension guidelines only. This includes utilizing home BP data before each visit [11] whenever available, which occurred in approximately half of the patients, but investigators were free to choose drugs according to their expertise, and specific instructions on choice of drugs were not given in order to avoid confounding the trial by an 'intervention in the intervention' bias [12]. When specifically interviewed on the how drugs were selected for each patient, including choice of diuretics, use of diuretics, the participating investigators emphasized that their choice of drugs in the control group was made based on their evaluation of the specific clinical profile of individual patients. IHM measurements were taken also in the control group but investigators treating the patients were blinded for these data which were not utilized.

Office and ambulatory blood pressure measurements

Patients were followed with office BP measurements at 1, 2, 4 and 6 months, whereas ABP measurements were performed at baseline before randomization and at 6 months follow-up. In each center, all patients and all BP measurements during follow-up were handled by the same physicians using the same calibrated and validated devices. Both

Hemodynamic status	Antihypertensive drug			
Vasoconstriction	If +34 to +100%, then use **normal dose** of CCB-DHP, ACEI, ARB		If > +100%, then use **high doses** of CCB-DHP, ACEI, ARB	
What to do	In each case: -if inotropy > +20%, then use CCB-DHP -if inotropy is normal (-20% to +20%) or low (i.e. hypo-inotropy, less than –20%), then use ACEI or ARB			
Hypervolemia	If normal (-20 to +20%), then no DIU		If high (> +20%), then use DIU	
What to do			If +20 to +50%, then use **normal** dose of DIU	If > +50%, then use **high** dose of DIU
Hyperinotropy	With normal volemia		With DIU-induced hypovolemia (< –20%)	
What to do	If +20% to +60%, then use VD-BB	If > +60%, then use non VD-BB	Stop DIU, Add CCB, ACEI or ARB Do NOT prescribe BB	
Hypoinotropy	Stop BB Prefer CCB-V or CCB-D rather than CCB-DHP			

FIGURE 2 Scheme for selecting and titrating antihypertensive drugs.

office and ABPs were measured by a validated oscillometric device (Microlife WatchBP O3; Microlife Health Management Ltd., Cambridge, UK).

ABPM was performed throughout a 24-h period with the device programmed to inflate and record BP at the following prespecified intervals: 15 min intervals from 0600 h to less than 2200 h (daytime) and 20 min intervals from 2200 h to less than 0600 h (night-time). It was *a priori* decided that at least 70% valid measurements were required. During ABPM patients were asked to refrain from unusual and/or intense physical activities.

Office BP measurements were performed three times with the patient in a sitting position, with 1 min interval between them. The first measurement was excluded whereas the mean value of the second and third measurements was calculated as office BP value. Oscillometric BP measurements with the same device were performed also during impedance cardiography by the HOTMAN system.

Normalization of BP was defined as BP levels at month 6 below following thresholds: daytime SBP <135 mmHg, office SBP <140 mmHg, night-time SBP <120 mmHg, 24 h SBP <130 mmHg, daytime DBP <85 mmHg, office DBP <90 mmHg, night-time DBP <70 mmHg, or 24 h DBP <80 mmHg, according to the 2007 ESH Guidelines. Visit-to-visit variability (VVV) was calculated as the standard deviation (SD) of the average of office BP values from baseline to study end.

Adverse events and quality of life

Adverse events were regularly investigated actively at each visit, by giving participants a written self-questionnaire (Figure 1, online data supplement, http://links.lww.com/HJH/A528) in which 30 common adverse events related to antihypertensive drugs were proposed in a neutral order for the purpose of catching the data. Quality of life was assessed at each visit by a visual analog scale.

Adverse event was defined as any untoward medical occurrence in a patient administered with a pharmaceutical product (both the HOTMAN monitoring and selected drugs) and which did not necessarily have a causal relationship with this product. The relationship of an adverse event to the selected drugs was graded as definite, probable, possible, unlikely, and unrelated. The severity of an adverse event was graded as mild (discomfort noted, but no disruption of normal daily activity); moderate (discomfort sufficient to reduce or affect normal daily activity), or severe (instability to work or perform normal daily activity). A serious adverse event was any untoward medical occurrence that results in death or was life-threatening, evaluated by investigators as yes or no.

To better reflect the nature of the health problem occurring to the included patients and the purpose of this study, endpoints of special interest were also defined as the endpoints including atrial fibrillation, myocardial infarction, palpitations, tachycardia, chest pain, edema, blood creatinine increase, gout, hyperkalemia, syncope, or renal impairment.

Number and type of prescribed antihypertensive drugs was also recorded at each visit.

Study flow and masking of investigators

All primary and secondary efficacy variables (ABPM data, office BP data, IHM data, PWV, central BP, and echocardiographic data) were measured by nurses, technicians, engineers, or physicians, but independently of the medical care of the patients.

In both IHM group and the control group, ABPM and echocardiography measurements were done at baseline and at 6 months, whereas hemodynamic assessment, office BP measurement, home BP monitoring and PWV measurements were done at baseline and at every follow-up visit (Fig. 3). In both groups, physicians had all possibilities of selecting antihypertensive drugs, according to 2007 ESH-ESC

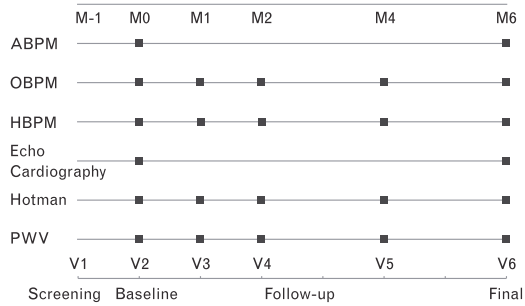

FIGURE 3 Schedule of the tests at each visit.

Guidelines, and based on office BPM, home BPM and on ABPM at randomization visit. Only in the IHM group were all results of hemodynamic measurements immediately available to the physician and they were masked to the (same) physician in the control group. In both control and IHM groups, the results of the PWV measurements were masked to the physician.

Treatment was titrated according to the values of office SBP and, when available, home SBP (baseline and follow-up) and ABPM SBP (baseline). In adapting treatment, the physician took into account several parameters (Fig. 2), among which the target office SBP of less than 140 mmHg was the most important one. Among the various parameters, which were most useful to the physician to take decisions related to titration, office SBP and SBP values obtained during the hemodynamic assessment were those most frequently taken into account.

Monitoring and data handling

The study was monitored by Sintesi Research (Milan, Italy), an independent company with no relationship to the sponsor. Sintesi Research monitored each site according to standard GCP, assembled all baseline characteristics of patients, office BP, home BP, ABP, IHM and other clinical data collected during follow-up, and cleaned queries prior to transferring data to the central data base in Milan, and before locking of the data base prior to any statistical analysis.

All impedance cardiography measurements and ABPs were stored together with all the assembled data in a centralized database at Istituto Auxologico Italiano, Department of Cardiology, Milan, Italy. All statistical work included in this article was done by professional independent medical statisticians (P.R., X.L., M.G.V.) in University of Milano-Bicocca.

Statistical analysis

The sample size was calculated to detect a different decrease of ambulatory daytime SBP from baseline to study end between IHM and classical drug selection group. One hundred and eight individuals per group were required to detect a difference of 5 mmHg with 80% power at a type one error of 5% in a two-sided *t*-test, assuming a SD of 13 mmHg. To end up with 108 individuals per group it has been recommended to enroll 250 participants and randomize 125 participants per group.

Full analysis set including all randomized individuals who had the assessment of the primary endpoint, was used for the efficacy analyses. An analysis set with all randomized individuals who had at least one safety assessment at a follow-up visit was used for safety analyses. Variables are summarized by treatment group as means with SD for continuous data, and as absolute numbers and their frequencies for categorical data. BP changes are BP at month 6 minus baseline (negative means decrease) and their 95% confidence intervals, among which the ambulatory SBP change was the primary endpoint. The primary endpoint was evaluated by two-sample *t*-test. A linear regression model on ambulatory SBP at month 6, adjusting for the baseline ambulatory SBP value, center, sex, age and BMI, was applied to account for potential risk factors. The secondary endpoints on efficacy were evaluated using two-sample *t*-test on BP changes and chi-square test with one degree of freedom for the percentage of normalization of BP. Rate of fall (slope with time) in office BP over the five visits was analyzed by a longitudinal analysis. A mixed model was applied including (as response variable) all the BP measurements available from baseline to study end for each patient in the full analysis set. The dependence between measurements on the same individual was accounted for by the inclusion of a random intercept in the model. The model included the following: as regressors the visit number, the randomization arm, the interaction between the arm and visit number.

The visit-to-visit BP variability (VVV) was log converted before applying *t* test. The distribution of type of antihypertensive drugs (classified as agents acting on the renin–angiotensin system, β-blocking agents, CCBs, diuretics and others) at the study end was compared in the two arms by a chi-square test with four degrees of freedom.

The number of adverse events in each group was compared by a Poisson model, accounting for the total follow-up times in full analysis set. Incidence rate ratio (IRR) between IHM group and control group was computed on overall adverse events, serious adverse events, drug-related adverse events, endpoint of special interest and the severity of adverse events. Quality of life was compared by *t* test.

All tests were bilateral using $\alpha = 0.05$. Data were recorded in an SAS database and analyzed using SAS 9.2 (SAS Institute Inc., Cary, North Carolina, USA).

HOTMAN, PWV and echocardiography data and their analysis are not presented in this article and will be included in a subsequent publication.

RESULTS

Patients

Three hundred and fifteen patients were screened for the study. One hundred and forty-eight patients were excluded as a result of reasons summarized in the flow diagram in Fig. 4. The characteristics at baseline of the 167 UCH patients randomized to IHM-adjusted drug treatment ($n = 83$) and to classical clinical adjustment of medical treatment ($n = 84$) are compared in Table 1. Randomized patients included 102 men and 65 women from 28 to 84 years and their BMI was between 19.9 and 35.0 kg/m^2

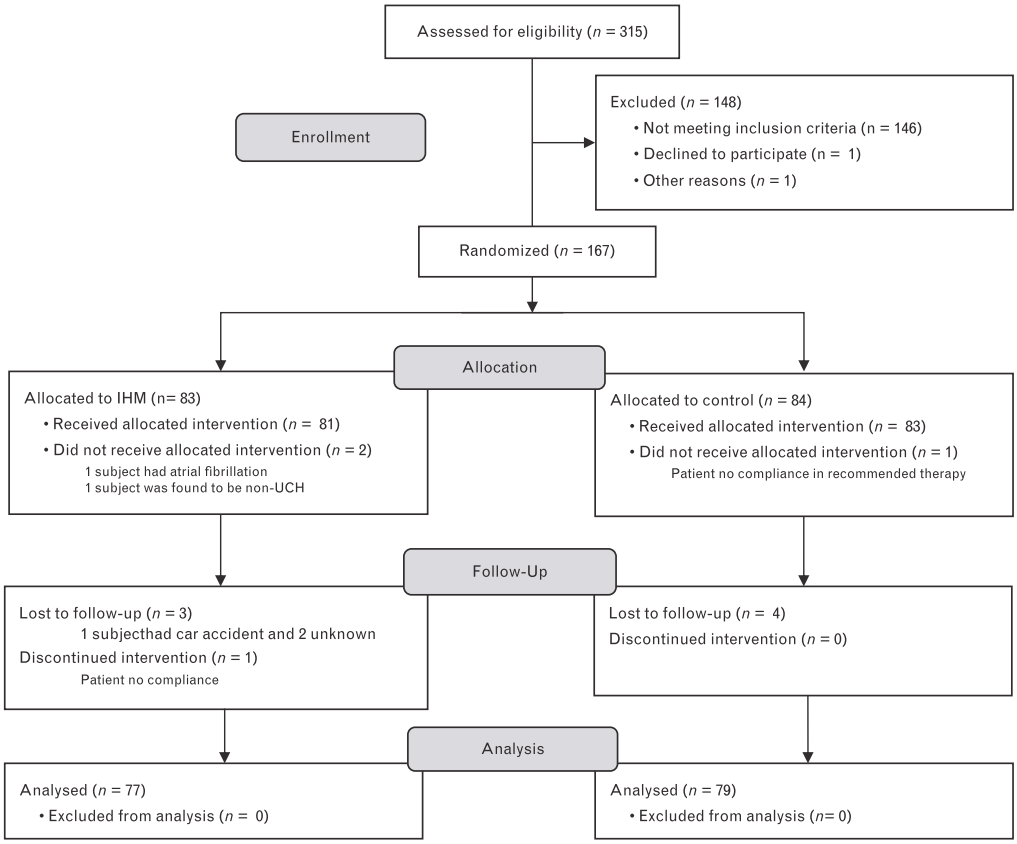

FIGURE 4 Patients flow diagram (The CONSORT).

with no significant differences between groups also in the subcategories of Table 1. There was no difference regarding demographic characteristics, disease history, comorbidities and number of antihypertensive drugs between groups.

Patients used tolerated doses of an average of 3.1 antihypertensive drugs (ranging from 2 to 7) (Table 1). Eighty patients from IHM group and 81 from control had at least one safety assessment at follow-up visit, and thus were included in safety analysis set. Among them, 77 in IHM and 79 in control group were followed-up to visit six and were included in the full analysis set (Table 2).

Blood pressure changes between study end and baseline, normalization rate at study end and visit-to-visit BP variability during follow-up

All the primary and secondary efficacy outcomes were evaluated in the full analysis set.

Mean daytime SBP by ABPM changed from 150.3 ± 11.6 and 149.9 ± 11.4 mmHg at baseline to 134.5 ± 12.0 and 134.5 ± 12.5 mmHg at study end in IHM and control group, respectively, with no difference (d) between the two groups, $d = -0.38$, 95% confidence intervals $= (-5.00, 4.25)$, $P = 0.87$. The linear regression model adjusting for baseline SBP, recruiting center, age, sex and BMI confirmed no difference between the two groups in ambulatory SBP at 6 months ($SBP_{IHM\text{-}control} = -0.29$, 95% confidence intervals $= (-3.90, 3.32)$ mmHg, $P = 0.87$).

Mean office SBP changed from 158.5 ± 19.9 and 155.1 ± 15.0 mmHg at baseline to 137.3 ± 15.5 and 137.9 ± 14.2 mmHg at study end in IHM group and control group, respectively, $d = -4.03$, 95% confidence intervals $= (-9.83, 1.78)$, $P = 0.17$. No between group difference in ABP and office BP changes between baseline and month 6 was found statistically significant.

The longitudinal office SBP values of each visit are presented in Fig. 5 by box plots separately for the two groups. Office SBP decrease with time was assessed by a mixed model including all the office SBP values from baseline to study end for each patient on the full analysis set. Both office SBP and DBP decreased significantly with visit [in the IHM group the decrease per visit was of -4.86 mmHg (95% confidence intervals: -5.76, -3.96) in SBP, and -1.69 mmHg (95% confidence intervals: -2.18, -1.20) in DBP; while in the control group the decrease per visit was of -3.98 mmHg (95% confidence intervals: -4.94, -3.03) in SBP and -1.49 mmHg (95% confidence intervals: -2.00, -0.98) in DBP, all $P < 0.0001$], whereas the difference between groups in the degree of BP reduction with visit was not statistically significant ($P = 0.18$ and $P = 0.56$ for SBP and DBP, respectively).

TABLE 1. Demographics of randomized individuals

		Total *N*	IHM group *N* (%)	Control group *N* (%)
All		167	83 (100)	84 (100)
No. of individuals by center	France	3	1(1)	2 (2)
	Italy	22	11 (13)	11 (13)
	Poland	37	16 (19)	21 (25)
	Estonia	52	29 (35)	23 (27)
	Norway	53	26 (31)	27 (32)
Sex	Male	102	53 (64)	49 (58)
	Female	65	30 (36)	35 (42)
Age (years)			64 (11)	62 (12)
BMI (categorical)	≤24.9	32	16 (19)	16 (19)
	25–29.9	66	38 (46)	28 (33)
	≥30	69	29 (35)	40 (48)
Ethnic race	Caucasian	164	82 (99)	82 (98)
	Black	3	1 (1)	2 (2)
Smoking habits (no. of cigarettes per day)	0 (nonsmoker)	149	76 (92)	73 (87)
	1–3	4	2 (2)	2 (2)
	4–6	5	4 (5)	1 (1)
	7–9	1	0	1 (1)
	≥10	8	1 (1)	7 (8)
Alcohol habits	0 (teetotal)	18	7 (8)	11 (13)
	Occasional	128	65 (78)	63 (75)
	1 drink/day	13	7 (8)	6 (7)
	2 drinks/day	7	4 (5)	3 (4)
	>2 drinks/day	1	0	1 (1)
No. of antihypertensive drugs at baseline (visit 2)	2	56	34 (41)	22 (26)
	3	49	20 (24)	29 (35)
	4	43	21 (25)	22 (26)
	5	12	6 (7)	6 (7)
	6	6	1 (1)	5 (6)
	7	1	1 (1)	0
SBP (mmHg)	Day SBP		150 (12)	150 (12)
	Night SBP		130 (14)	133 (15)
	24 h SBP		143 (11)	145 (12)
	Office SBP		157 (20)	156 (15)

Note: data are expressed as number (percentage) for categorical variables and mean (standard deviation) for continuous variables.

We also analyzed the difference between groups in the normalization rate of different BP measurements (Table 3). Although no significant difference between the IHM and control groups in normalization rate of 24 h and daytime ABP and office BP was found, the between group difference in nighttime DBP normalization was significant with a greater reduction with IHM ($P = 0.045$) which did not remain significant after multiplicity adjustment.

We further explored the VVV in full analysis set as the SD of average office SBP values over the various visits. VVV was 13.59 ± 6.99 and 13.02 ± 5.29 in IHM and control group, respectively, and the between group difference was not statistically significant ($P = 0.931$).

Number and type of drugs by visit in full analysis set

The average numbers of antihypertensive drugs used by patients included in full analysis set were 3.1, 3.8, 4.0, 4.1, 4.2 in IHM group from baseline to month 6 and 3.4, 3.8, 4.0, 4.1, 4.1 in control group, indicating a slight increase in number of drugs prescribed over follow-up time but without difference between the two groups. The number of

TABLE 2. Primary and secondary outcomes in full analysis set ($n = 156$)

Changes in BP (visit 6-visit 2)	IHM group ($N = 77$) Mean (SD)	Control group ($N = 79$) Mean (SD)	Diff (IHM–control) Mean (95% CI)	*P* (*t*-test)
Daytime SBP*	−15.8 (14.8)	−15.4 (14.5)	−0.38 (−5.00,4.25)	0.871
Daytime DBP	−6.8 (7.2)	−7.6 (8.1)	0.82 (−1.60,3.24)	0.504
Night SBP	−13.0 (16.8)	−10.6 (14.0)	−2.36 (−7.25,2.53)	0.341
Night DBP	−6.6 (8.5)	−5.7 (8.6)	−0.92 (−3.63,1.78)	0.501
24h SBP	−14.9 (13.9)	−13.1 (12.7)	−1.81 (−6.03,2.41)	0.398
24h DBP	−6.9 (6.5)	−6.5 (6.5)	−0.44 (−2.49,1.61)	0.671
Office SBP	−21.2 (20.6)	−17.2 (15.9)	−4.03 (−9.83,1.78)	0.174
Office DBP	−7.4 (10.0)	−6.3 (9.5)	−1.10 (−4.18,1.99)	0.483

Note: ''*'' is the primary outcome, the others are the secondary outcomes.

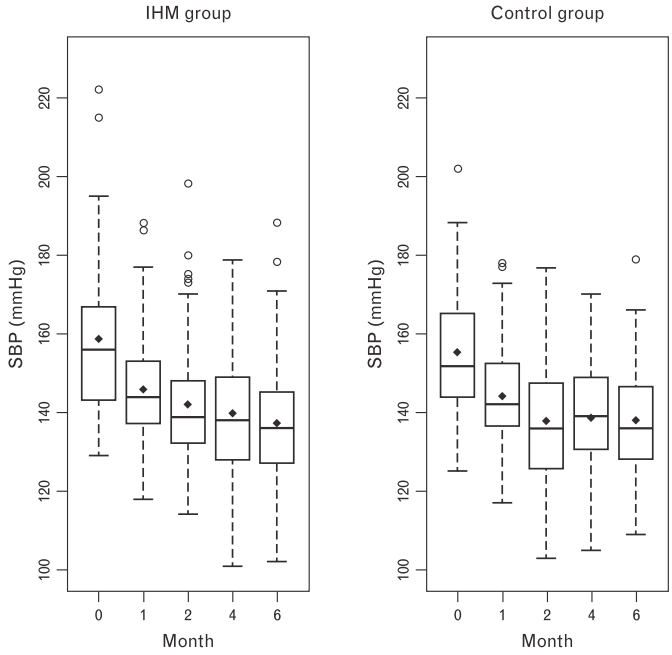

FIGURE 5 Office mean SBPs change by visit.

antihypertensive drugs decreased only in six patients from IHM group and in seven from control group. Although the distribution of drugs types was similar in the two arms at baseline, it was significantly different at the study end ($X_4^2 = 25.4$, $P < 0.0001$). In particular, the drugs most frequently used in both groups were agents acting on the renin–angiotensin system, counting for more than 40% of the total drugs used both at baseline and at study end. Frequency of CCBs was around 20% at baseline with a slight reduction at study end. Similar figures were found at baseline for β-blockers, which however showed a more evident tendency to be used less at study end only in IHM. Finally, from baseline to study end, the use of diuretics remained at a frequency around 15% in control group whereas it increased from 13 to 31% in IHM group. At 6 months, fractions of patients using diuretics were 41(52%) vs. 65 (84%), respectively, in the control and the intervention group. The number of patients taking at least one diuretic increased from 35 of 79 (44% at baseline) to 41 of 79 (52% at visit 6) in control group, and from 26 of 77 (34%) to 65 of 77 (84%) in IHM group (Table 4).

Safety analysis

The analysis of safety included 80 and 81 patients from IHM and control group, respectively. The mean number of adverse events in IHM and control group was compared, the IRR was 0.63 (95% confidence intervals: 0.45–0.89, $P = 0.008$) for total adverse events and 0.62 (95% confidence intervals: 0.41–0.93, $P = 0.021$) for drug-related adverse events, indicating a lower number of adverse events in IHM than in controls (Table 5). More detailed information about the type of adverse effects among groups is included in Table 6 and in Supplementary Table S3, http://links.lww.com/HJH/A528. In the latter table adverse

TABLE 3. Normalization of blood pressure at visit 6 in absolute number and percentage

Normalization of BP at visit 6	IHM group *N* (%)	Control group *N* (%)	*P* (Chi-square test)
All	77 (100)	79 (100)	–
Daytime SBP (<135 mmHg)	42 (55)	39 (49)	0.518
Daytime DBP (<85 mmHg)	63 (82)	62 (78)	0.602
Night-time SBP (<120 mmHg)	43 (56)	37 (48)	0.260
Night-time DBP (<70 mmHg)	60 (78)	50 (63)	0.045
24-h SBP (<130 mmHg)	42 (55)	39 (49)	0.518
24-h DBP (<80 mmHg)	62 (81)	57 (72)	0.219
Office SBP (<140 mmHg)	49 (64)	44 (56)	0.312
Office DBP (<90 mmHg)	71 (92)	73 (92)	0.963

Note: *N* is the number of patients whose BP was normalized, percentage is of those patients among their group.

TABLE 4. Number of patients with at least one prescription of agents acting on the renin–angiotensin system, β-blocking agents, calcium-channel blockers and diuretics at visit 6

Type of drugs	IHM group, *N** (%)	Control group, *N** (%)
All	77 (100)	79 (100)
Agents acting on the RAS**	74 (96)	78 (99)
β-blocking agents	32 (42)	47 (59)
Calcium-channel blockers	45 (58)	60 (76)
Diuretics	65 (84)	41 (52)

*N is the total number of patients who took at least one of the corresponding antihypertensive drugs at visit 6.
**RAS, renin–angiotensin system.

events are clustered according to organ system and listed alphabetically. As shown in all these tables, side-effects were less in the IHM than in the control group, including drug-related side-effects (Table 6). Absolute change in quality of life evaluated by VAS was compared in safety analysis set. The score increased from baseline to study end by 10.38 ± 21.26 in IHM group and 5.93 ± 18.94 in control group, the difference failing to reach statistical significance ($P = 0.164$). Similar results were yielded by analyses carried out in full analysis set (data not shown).

DISCUSSION

We evaluated 315 patients with UCH, excluded 148 patients who did not fulfill inclusion criteria, and further investigated 167 patients who had UCH verified by ABP measurements. They were prospectively randomized to noninvasive integrated hemodynamic monitoring-guided drug adjustments vs. classical clinically adjusted drug treatment in five European Hypertension Excellence centers. During 6 months of follow-up in both groups, office BP and ABP decreased to similar marked extent, with a reduction of SBP equal or greater than 15 mmHg in both arms. The use of diuretic treatment was higher and the adverse events during the follow-up months were significantly less in IHM group.

Antihypertensive drug adjustment based on integrated hemodynamic management

In all participants of our study antihypertensive medications were adjusted according to ESH/ESC hypertension guidelines. However, although in the control group this was done in a conventional manner, based on the clinical expertise of doctors working in the European Hypertension Excellence centers involved, in the IHM group treatment adjustment was guided by impedance cardiography through the HOTMAN system [8,9]. Impedance cardiography is a noninvasive hemodynamic diagnostic and monitoring technology that has demonstrated its usefulness and reproducibility during the last years [13–16] in various populations, including patients with hypertension and/or coronary artery disease. Preliminary data suggest that, when the selected pharmacological class of antihypertensive agent does not correspond to the patient's hemodynamic state, BP reduction is limited, BP fall is delayed, and side-effects may occur more frequently. By contrast, the available data also suggest that, when the pharmacological class of antihypertensive treatment is adapted to the hemodynamic state (for instance, diuretics for hypervolemia; calcium antagonists, angiotensin converting enzyme inhibitors or α-receptor blockers for increased peripheral resistances; β-blockers for hyperinotropy), BP reduction occurs more rapidly and to a greater extent. This evidence has been obtained in patients with resistant hypertension [8], and in patients with mild to moderate hypertension [17–19]. The value of using impedance cardiography-derived hemodynamic data as an adjunct to therapeutic decision-making in the treatment of hypertension has been supported in a meta-analysis [18], which demonstrated that impedance cardiography-based approaches are in keeping with previously advocated strategies which incorporate patient-individualized drug regimens, evidence-based medicine, and practical, easy to apply, cost-effective principles to further improve hypertension control rates.

However, previous studies on this issue were based on impedance cardiography devices characterized by a questionable accuracy in defining patients' hemodynamic state [20,21]. Conversely, ours is the first study addressing this issue through the use of HOTMAN system, which was independently validated in its ability to quantify the hemodynamic status in comparison with invasive assessments based on the thermodilution technique [9]. Moreover, the HOTMAN system allows a complete noninvasive assessment of patient's hemodynamics with two important improvements compared with other previous devices: the safer use of a very low current, and the use of a new data signal processing along with an improved mathematical algorithm for more precisely characterized hemodynamic status, as described in the 'Methods' section [10].

TABLE 5. Mean number of adverse events in safety analysis set

Type of adverse event	IHM group Mean (SD)	Control group Mean (SD)	Poisson model IRR* (95%CI)	Poisson model *P* value
No. of overall adverse events	1.18 (1.17)	1.91 (2.09)	0.63 (0.45–0.89)	0.008
No. adverse events of endpoint special interest**	0.31 (0.61)	0.31 (0.54)	1.04 (0.59–1.84)	0.896
No. drug-related adverse events	0.74 (0.96)	1.22 (1.66)	0.62 (0.41–0.93)	0.021
No. serious adverse events	0.11 (0.36)	0.23 (0.58)	0.49 (0.20–1.17)	0.110
No. severe adverse events	0.05 (0.22)	0.04 (0.19)	0.99 (0.61–1.63)	0.979

*IRR, incidence rate ratio.
**Endpoint special interest includes atrial fibrillation, myocardial infarction, palpitations, tachycardia, chest pain, edema, increased serum creatinine, gout, hyperkalemia, syncope, renal impairment.

TABLE 6. Overall number of side-effects as listed according to the questionnaire in the protocol

Adverse event	Randomization Group		All
	IHM group	Control group	
1. Feeling tired/weakness	15	9	24
2. Stomach upset	4	6	10
3. Nausea/vomiting	0	7	7
4. Diarrhea	1	1	2
5. Constipation	1	6	7
6. Changes in taste or appetite	1	1	2
7. Thirst	0	1	1
8. Changes in weight	0	1	1
9. Trouble heart beating (tachycardia/bradycardia)	8	7	15
10. Symptoms during effect	0	0	0
11. Thoracic pain	3	10	13
12. Headache	3	9	12
13. Dizziness/lightheadedness	7	13	20
14. Blackout	1	4	5
15. Dry mouth/eye	1	5	6
16. Rash/itching	2	8	10
17. Flushing	0	1	1
18. Edema	4	9	13
19. Trouble breathing	5	8	13
20. Dry cough	1	7	8
21. Sexual problems	1	2	3
22. Raynaud phenomenon	1	2	3
23. Muscle cramps	4	5	9
24. Bruising	0	0	0
25. Swarming/pricking sensations	2	0	2
26. Eyesight changes	0	1	1
27. Yellow eyes or skin	0	0	0
28. Sleep disturbance	1	5	6
29. Mood swings	0	1	1
30. Others	28	26	54
All	94	155	249

Our study also adds to previous studies managing hypertension through other different approaches, such as the randomized BP GUIDE Study, which used central BP as a guide for treatment [22]. Although this approach is also of interest, it has to be emphasized that, given the difficulties in calibrating central BP, its actual clinical applicability is highly questionable, at variance from the approach followed in our study, based on a more solid hemodynamic assessment for drug selection.

Considerations on our findings

A question which needs to be addressed while interpreting our results is why, in spite of the theoretical advantages of a drug selection and titration based on IHM, no difference in the reduction and normalization of daytime ambulatory and office BP was observed between the IHM and control group. Although our study cannot provide a definite explanation for this finding, it might have been influenced by the relatively moderate number of participants we could recruit. However, we recruited numbers close to those used for statistical power analysis and results were virtually identical supporting no true differences. We speculate that, at least in part, this lack of superiority of IHM vs. control depends on the fact that in our study patient management was carried out by experienced doctors working in five European Hypertension Excellence centers. This implies that, even in the control group, drug selection and titration was done with accuracy, which may have minimized the between group differences in achieved BP.

We found that adverse events were significantly less in IHM than in control group. Though most adverse events were of the more general type and not necessarily related to drug treatment for hypertension (Table 6), our data suggest that matching drug choice with the individual hemodynamic profile is likely to have favored an overall reduction in side-effects, and thus made treatment more acceptable. This result may also suggest that choice of antihypertensive treatment based on patient's hemodynamic profile may lead to administration of more acceptable and better tolerated drugs, which may favor patients' compliance and in the end, improve hypertension control. Along the same line we find it interesting that IHM-based approach led to a significantly different choice of antihypertensive drugs during follow-up as compared with controls, in particularly to a higher use of diuretics and lower use of β-blockers, with no significant differences in the prescription of other drug classes. We may speculate that such changes in medication may be related to the concomitant finding of less unspecific adverse events.

Intentionally we did not recruit a population with 'treatment-resistant hypertension' which would mandate treatment with diuretic, and we did not write a protocol which made it mandatory to use a diuretic. Moreover, given that guidelines are not rules, the lead investigators made their choices according to their clinical experiences and feelings for right choices for individual patients. At 6 months, fractions of patients using diuretics were 41 (52%) vs. 65 (84%), respectively, in the control and the intervention group, which probably enhanced the likelihood of showing a difference in BP between groups. Diuretics were 13% out of all the drugs used, but the number of patients taking at least one diuretic increased from 35 of 79 (44% at baseline) to 41 of 79 (52% at visit 6) in control group, and from 26 of 77 (34%) to 65 of 77 (84%) in the IHM group. Despite this finding the control group did as well as the IHM group regarding BP control at 6 months – making this a 'neutral' study.

It is an interesting point to note that the use of diuretic was limited to 52% of patients in the control group whereas the ESH guidelines recommend diuretic in most drug combinations. We have no further detailed explanation for this finding except that this is 'clinical practice' even in ESH hypertension specialist centers, and that the drug choice was based on assessment of individual clinical profile also in the control group.

In as much as the study was neutral, in other words the Nil hypothesis was confirmed, we cannot recommend applying IHM (HOTMAN) measurements in clinical practice based on our data. Therefore, we abstain from speculating further on potential difficulties in including IHM in clinical practice or discussing the cost of each IHM measurement.

Study limitations

We have to acknowledge a few limitations of our study. First, we could not achieve the preplanned sample size. However, the number of analyzed volunteers was high

enough to maintain statistical power and we virtually had no differences in office and ABPs between groups strongly supporting the main findings. Second, our study was carried out, as already mentioned, in European Hypertension Excellence centers, and the patient care they have provided may not fully reflect what happens in general practice. It would be interesting in the future to explore whether in general practice there is indeed a greater benefit in having treatment guided by IHM (HOTMAN) in UCH. Third, though the lead investigators were in principle blinded for the IHM (HOTMAN) readings in patients in the control arm, it is possible that information may have leaked from technician or patient to physician, in as much as IHM readings were open for technician and to some degree also for patients. In this regard, the fact that the same doctor was responsible for the treatment of patients in both arms might have carried a potential bias. Fourth, in spite of the technological improvement in the HOTMAN system and of its validation against invasive hemodynamic studies, also the noninvasive method we used is likely to have been somehow affected by the known intrinsic problems of impedance cardiography, which may have limited the accuracy of patient's hemodynamic assessment.

In conclusion, our findings show that noninvasive monitoring of hemodynamic parameters associated with a predefined algorithm of drug selection does not contribute to improved BP control in European Hypertension Excellence centers and induce similar reductions in 24 h and daytime ABP and in office SBP, as compared with conventional clinical drug selection in patients with UCH. However, IHM-guided hypertension management was associated with larger use of diuretics in response to hemodynamic need, and with fewer unspecific adverse events. Despite a neutral study with no BP difference between the two arms, we believe that the IHM-guided management should be further investigated under less strict conditions in daily practice.

Perspectives

We did the first ever prospective and randomized comparison of IHM-guided treatment vs. clinical drug adjustment in patients with UCH. Our main findings were that office and daytime BP control through 6 months were virtually identical when using IHM drug adjustment as compared with best practice treatment. The use of IHM led to more use of diuretics in treating patients with UCH and this was associated with a lower rate of unspecific adverse events. Thus, although our data do not support the recommendation to use IHM in routine clinical care, they do support the need of further research on this approach, to identify conditions where it might be clinically useful.

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Conflicts of interest

F.E.M.F.E. has received lecture honoraria from Medtronic and Hemo Sapiens. A.C.L. has received lecture honorarium from Hemo Sapiens and MSD. S.E.K. has received lecture honoraria from AZ, Bayer, Medtronic, MSD, Novartis and Takeda, honoraria for consulting from Bayer, Medtronic, Takeda and Serodus, and research support from AZ and Pronova. M.G.V. has received lecture honoraria from AZ, Boehringer Ingelheim, Servier, Abbott and MSD. G.P. has received lecture honorarium from Hemo Sapiens, Daichii-Sankyo, Omron, and Servier. S.L. has received lecture honoraria from Daichii-Sankyo, Novartis, Omron, and Servier, and research support from Atcor, Esaote Pie Medical, and Servier. The other authors have no disclosures.

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Reviewers' Summary Evaluation

Reviewer 1

The main strength of this article is that it is the first randomized clinical trial to investigate the potential utility of a particular electric thoracic bioimpedance device, 'HOTMAN' (IHM), for the control of hypertension in clinical practice. The main weakness is that the control group was not clearly treated according to ESH guidelines, specially regarding the use of diuretics in uncontrolled hypertensive patients.

Despite this, there were no differences in BP control between the two arms. The fewer adverse effects in the IHM group were only partly justified by differences in drugs used in the two groups.

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ORIGINAL ARTICLE

Non-invasive hemodynamic monitoring as a guide to drug treatment of uncontrolled hypertensive patients: effects on home blood pressure in the BEAUTY study

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ABSTRACT

Background: In the BEAUTY study we investigated whether utilizing non-invasive monitoring of hemodynamic parameters combined with a drug selection algorithm (integrated hemodynamic management-IHM) compared to conventional drug selection may improve home BP in patients with uncontrolled hypertension.

Methods: Uncontrolled (office systolic blood pressure (SBP) > 140 mmHg and ambulatory daytime SBP >135 mmHg while taking ≥2 antihypertensive drugs) essential hypertensive patients were referred to 5 European Hypertension Excellence Centers and, if eligible, were randomized into IHM-guided vs conventional treatment adjustment. Home blood pressure (BP) was taken with 2 repeated readings at 1–2 min intervals in the morning and in the evening (before drug intake and eating) during the week preceding the visit at the outpatient clinic after 5 min rest using a validated semi-automatic oscillometric arm cuff device and with a correct cuff bladder placement. Home blood pressure was measured in a sub-group of patients ($n = 84$) not significantly different from the other patients.

Results: Home SBP changed from 152.1+/−15.8 and 149.8+/−11.8 mmHg to 131.0 +/−11.1 and 139.6+/−12.8 mmHg in IHM group ($n = 46$) and Control group ($n = 38$), respectively, showing significantly greater reduction in IHM than in Control group (d= −10.9 mmHg, 95% CI −17.77, −4.02), $p = 0.002$. The reduction remained significant after multiple adjustments, particularly for baseline home SBP, recruiting center, age, sex and BMI ($SBP_{IHM\text{-}Control}$= −9,63 mmHg, 95% CI −14.28, −5.11) mmHg, $p < 0.0001$).

Conclusion: Drug selection algorithm based on non-invasive hemodynamic monitoring induced larger reduction in home BP compared to conventional drug selection in uncontrolled hypertensive patients referred to European Hypertension Excellence Centers. Although the main BEAUTY study was negative, these home BP measurements taken by patients themselves may suggest that the integrated hemodynamic monitoring is useful in patients with uncontrolled hypertension. This finding might depend on specific features of home BP measurements which could make it recommended BP measurement method for drug trials.

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Antihypertensive drugs; blood pressure control; integrated hemodynamic monitoring; uncontrolled hypertension; home blood pressure monitoring

Introduction

Appropriate control of BP is essential for prevention of future cardiovascular events. However, BP control among treated hypertensive patients is generally considered as insufficient. There is growing evidence linking hypertension to altered hemodynamic modulators [1]. Better selection of antihypertensive drugs, guided by non-invasive integrated hemodynamic management (IHM) using impedance cardiography, may possibly counteract such problems and provide better BP control [2,3]. In the BEAUTY study [4] non-invasive hemodynamic monitoring associated with a drug selection algorithm induced similar reductions in ambulatory daytime and office SBP compared to conventional drug selection.

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Recently, the usefulness of self-measured BP at home (home BP measurement) for the management of hypertension has been reported in many studies. When compared with office BP, home BP yields multiple measurements over several days taken in the individual's usual environment and is more widely available [5]. A large systematic review has demonstrated that home BP is a significant predictor of cardiovascular mortality and cardiovascular events and an important prognostic variable over and above that of office BP [6].

Thus, the aim of the present study was to explore whether IHM improves the blood pressure control according to home BP measurements and test the hypothesis that difference may be visualized better with home BPs.

Materials and methods

Study design, patients and objectives

The BEtter control of blood pressure in hypertensive pAtients monitored Using the HOTMAN® sYstem (BEAUTY) Study was an investigator initiated and driven multicenter prospective randomized parallel groups controlled study with sites at five Excellence Centers of the European Society of Hypertension (ESH), Gdansk (Poland), Milan (Italy), Oslo (Norway), Paris (France), and Tallinn (Estonia), ClinicalTrials.gov Identifier: NCT01482364. The study was overseen by a steering committee consisting of the five senior investigators representing all sites (SEK, MV, KN, GP, SL).

Primary objective was to explore whether monitoring hemodynamic parameters and then applying a predefined algorithm of drug selection (i.e. IHM) with the HOTMAN® System improves the control of daytime SBP at ambulatory blood pressure monitoring (ABPM) in hypertensive patients, as compared to classical drug selection (i.e. without IHM) during a 6 month intensive treatment program. One of the secondary objectives was to explore whether IHM improves the blood pressure control according to home BP measurements, which is the focus of the current paper.

Patients aged 18–85 years of either gender were referred from general practices responding to letters of invitation or were recruited directly by newspaper advertisements or referrals to the university outpatient clinics. They were worked-up at the five participating university hospitals in the time period from January 2011 through December 2012 by experienced physicians. Of the 315 screened patients 167 met the inclusion criteria and were randomized [6] and outcome was available for 156 patients (full analysis set). Among these 156 patients, 84 (54%) entered into the substudy that included also home blood pressure measure (HBPM). This subgroup was not significantly different from the subgroup without HBPM. Oslo center did not do home BP as it was not mandatory in the main protocol.

UCH was defined as elevated office SBP (>140 mmHg) despite regular intake of 2–4 or more antihypertensive drugs (towards the end of recruitment we accepted up to 7 drugs but in few patients only, which is reflected by a total average of 3 drugs). Additionally, patients had to qualify by also having mean ambulatory daytime SBP >135 mmHg. Drug treatment was unchanged for two weeks and no other change in medication was pre-planned for the following 6 months.

The study was approved by all relevant committees for clinical research ethics in the participating countries and by the institutional research committee of all 5 hospitals. All patients gave written informed consent for participation and publication of results. All patients who qualified for the procedure within the 24 month time period were included. Expenses were mostly covered by the hospitals and partly by grants-in-aid from one sponsor (Hemo Sapiens Inc. European Office, Bucharest, Romania), and patients were not paid.

Patients were randomized using a pre-determined 2×2 randomization list through a website organized by the monitor of the study (Sintesi Research, Milan, Italy).

Home BP measurements

Home BP was available in 46 IHM and 38 controls at the beginning of the study and at 6 months. Home BP was measured for one week before each study visit. Home BPM was done according to the 2008 European Society of Hypertension (ESH) home BP monitoring guidelines [7]: a) with 2 repeated readings at 1–2 min intervals in the morning and in the evening (before drug intake and eating); b) during the week preceding the visit at the outpatient clinic; c) after 5 min rest and 30 min without smoking or caffeine, seated, back supported, immobile, legs uncrossed, not talking, relaxing, arm resting on the table; d) using a validated semi-automatic oscillometric arm cuff device and with a correct cuff bladder placement; e) a written report of BP values was provided to the physician during the outpatient clinic

visit; and f) the first day of each weekly session was discarded. Home SBP and DBP (diastolic blood pressure) were determined as the average of all remaining morning and evening values for the period considered. The effects of each management strategy were assessed by comparing the home BP values obtained in two occasions, i.e. before the randomization visit and before the last visit, scheduled.

Validated home BPM device based on the same software, such as the Microlife Watch-BP device, which also offered the possibility to perform and store home BP measurements following the 2008 ESH home BPM guidelines. Home BP measurements were not performed on all patients in the study due to shortage of devices in some centers and due to home BP being a secondary endpoint and not obligatory in the protocol.

Impedance cardiography with the HOTMAN® (hemodynamic & oxygen transport management) system

The HOTMAN® system allows a non-invasive assessment of patient's hemodynamics with two important improvements compared with other previous similar devices: (i) use of a very low current (7 μA, 300–400-fold lower than that used by other products, making it safer for the patient), and (ii) use of a new data signal processing and of an improved mathematical algorithm. The system has been validated against an invasive thermodilution approach [3].

Recordings by the HOTMAN® System are performed with patients in the supine position, resting for 5 minutes before measurement and involve non-invasive measurement of thoracic impedance through placement of four pairs of thoracic electrical bio-impedance specific sensors placed on the neck and lower thorax. Electrical impedance changes are digitally processed to calculate different hemodynamic parameters. Compared to classical 'impedance cardiography' the HOTMAN® system has some different characteristics. It measures SVRI per beat, i.e. SSVRI (Stroke systemic vascular resistance index), an index of vasoactivity, which is not detected by classical systems.

Adjustments of drug treatment which could be done by changing either class of medication or their doses, were then performed in the IHM group under the guidance of a pre-specified algorithm according to patients vascular resistance, volemia and/or inotropy [7] (Table 1).

Conversely the control group had their antihypertensive medication adjusted at baseline, 1 month and at 3 months by lead investigators in each site according to 2013 ESH/ESC hypertension guidelines [8] only. This includes utilizing home BP data whenever available in approximately half of the patients but investigators were free to choose drugs according to their expertise and specific instructions on choice of drugs were not given in order avoid confounding the trial by an 'intervention in the intervention' bias [9].

Monitoring and data handling

The study was monitored by Sintesi Research (Milan, Italy), an independent company with no relationship to the sponsor. Sintesi Research monitored each site according to the GCP standard, and cleaned queries prior to transferring data to the central database in Milan, and before locking of the database prior to any statistical analysis.

All impedance cardiography measurements and ambulatory BPs were stored together with all the assembled data in a centralized database at Instituto Auxologico Italiano, Department of Cardiology, Milan, Italy. All statistical work included in this paper was done by professional independent medical statisticians (PR, XL, MV) in University of Milano-Bicocca.

Statistical analysis

Descriptive statistics, including means, standard deviations, and frequencies, were used to summarize the patients characteristics. Characteristics of patients with and without HBPM were compared by Chi-square test and t-test for categorical and continuous variable, respectively. Fisher's exact test was used when there was at least one cell with expected count less than 5.

The difference among the two arms on HBPM, ABPM and OBPM were evaluated using two-sample *t*-test on BP changes from baseline to follow-up. Chi square test with one degree of freedom was used to compare the percentage of normalization of BP.

A linear regression model on HBPM and ABPM at follow-up (M6), adjusting for the baseline home SBP, was applied to account for centers and potential risk factors (sex, age, BMI) in the estimate of treatment effect. Rate of fall (slope with time) in OBPM was analyzed separately by a longitudinal analysis. A mixed model was applied including (as response variable) all the BP measurements available from baseline to M6 for each patient on the secondary analysis set (with at least two measurement available and assuming missing at random). The fit of a linear (decreasing) trend by visit was checked by a spaghetti plot. The dependence between

Table 1. Scheme for selecting and titrating antihypertensive drugs.

	Antihypertensive drug		
Vasoconstriction	If +34 to +100%, then use **normal dose** of CCB-DHP, ACEI, ARB		If > +100%, then use **high doses** of CCB-DHP, ACEI, ARB
What to do	In each case: -if inotropy > +20%, then use CCB-DHP -if inotropy is normal (−20% to +20%) or low (i.e. hypo-inotropy, less than −20%), then use ACEI or ARB		
Hypervolemia	If normal (−20 to +20%), then no DIU		If high (>+20%), then use DIU
What to do			If +20 to +50%, then use **normal** dose of DIU / If > +50%, then use **high** dose of DIU
Hyperinotropy	With normal volemia		With DIU-induced hypovolemia (<−20%)
What to do	If +20% to +60%, then use VD-BB	If > +60%, then use non VD-BB	Stop DIU, Add CCB, ACEI or ARB Do NOT prescribe BB
Hypoinotropy	Stop BB Prefer CCB-V or CCB-D rather than CCB-DHP		

Table 2. Demographics of subjects who had home BP at both V2 and V6.

		Yes			No	*P*-value of χ^2 comparing pts with and without HOME BP
HOME BP measurement:		Total N pts	IHM group N (Percentage, %)	Control group N (Percentage, %)	Total N pts	
All		84	46(100)	38(100)	72	
No. of subjects by Center	France	1		1(3)	2	<0.001[a]
	Italy	10	6(13)	4(11)	9	
	Poland	24	12(26)	12(31)	10	
	Estonia	49	28(61)	21(55)	1	
	Norway	0			50	
Sex	Male	45	24(52)	21(55)	48	0.0966
	Female	39	22(48)	17(45)	24	
BMI continuous, kg/m2	Mean (standard deviation)	30(4)	30(4)	30(4)	29(4)	0.1632[b]
BMI categorical	≤24.9	13	6(13)	7(18)	14	0.1661
	25–29.9	28	20(44)	8(21)	32	
	≥30	43	20(44)	23(61)	26	
Race	Caucasian	84	46(100)	38(100)	69	a 0.0961
	Black	0			3	
Smoking habits	0 (non-smoker)	78	44(96)	34(90)	62	0.3243
	1–3	1	1(2)	–	3	
	≥4	5	1(2)	4(11)	7	
Alcohol habits	0 (teetotal)	8	4(9)	4(11)	9	0.3469a
	occasional	69	38(83)	31(82)	52	
	1 drink/day	3	2(4)	1(3)	7	
	2 drinks/day	4	2(4)	2(5)	3	
	>2 drinks/day	0			1	
No. of antihypertensive agents at baseline (Visit 2)	Mean (standard deviation)	3.2(1.1)	3.0(1.0)	3.4(1.1)	3.2(1.0)	0.7491b

[a]Fisher exact test.
[b]t-test.
Note: data are expressed as number (percentage) for categorical variables and mean (standard deviation) for continuous variables.

measurements on the same subject was accounted for by the inclusion of a random intercept in the model. The model included as regressors the visit number/time of the visit, the randomisation arm, the interaction between the arm and time and other potential risk factors.

All tests were bilateral using $\alpha = 0.05$. Data were recorded in a SAS database and analyzed using SAS 9.2.

Results

Patients

The characteristics at baseline of 84 uncontrolled hypertension (UCH) patients randomized to IHM adjusted drug treatment ($n = 46$) and to classical clinical adjustment of medical treatment ($n = 38$) are compared in Table 2. There was no difference

Table 3. Home blood pressure values and control rates at 6 months.

Changes in HMBP (visit 6-visit 2)	IHM group (N = 46) Mean (SD)	Control group (N = 38) Mean (SD)	Diff (IHM-Control) Mean (95% CI)	*P*-value
Home SBP	−21.1 (17.7)	−10.2 (13.0)	−10.90 (−17.77, −4.02)	0.002
Home DBP	−7.6 (9.0)	−6.9 (10.6)	−0.67 (−4.91, 3.58)	0.756
SBP and DBP normalization at 6 months	*n (%)*	*n (%)*		
Home SBP(<135 mm Hg)	30 (65%)	12 (32%)		0.002
Home DBP(<80 mmHg)	34 (74%)	27 (71%)		0.770

regarding demographic characteristics, disease history and number of antihypertensive drugs between groups. Patients used tolerated doses of an average of 3.2 antihypertensive agents (ranging from 2 to 6). Mean number of agents per patient has increased during the study by 0.7 ± 1.09 in the IHM group and 0.5 ± 0.95 in the Control group.

Office, ambulatory and home blood pressure changes between study end and baseline

In the subgroup of patients with HBPM, mean office SBP changed from 159 ± 23 and 155 ± 16 at baseline to 140 ± 17 and 140 ± 16 mmHg at study end in IHM group and Control group, respectively (d= −4.08 mmHg, 95% CI −12.81;4.65, $p = 0.36$). In the same subgroup, mean day-time SBP by ABPM changed from 148 ± 12 and 149 ± 10 mmHg at baseline to 133 ± 12.0 and 133 ± 12 mmHg at study end in IHM and Control group, respectively, with no difference (d) between the two groups (d= −0.58 mmHg 95% CI −6.11;7.28, $p = 0.86$). The linear regression model adjusting for baseline SBP, recruiting center, age, sex and body mass index (BMI) confirmed no difference between the two groups in ambulatory SBP at 6 months ($SBP_{IHM\text{-}Control} = -0.93$ mmHg, 95% CI −5.9; 4.05 mmHg, $p = 0.72$).

Home blood pressure changes between study end and baseline and control rates at study end, are demonstrated in Table 3.

Home BP displayed at 6 months a significantly greater reduction in IHM (−21.1 ± 17.7 mmHg) than in controls (−10.2 ± 13.0 mmHg, $P = 0.002$). Home SBP changed from 152.1 ± 15.8 and 149.8 ± 11.8 mmHg to 131.0 ± 11.1 and 139.6 ± 12.8 mm Hg in IHM group and Control group, respectively, showing significantly greater reduction in IHM than in Control group (d= −10.9 mmHg, 95% CI −17.77, −4.02, $p = 0.002$, Table 3), which remained significant after multiple adjustment particularly for baseline home SBP, recruiting center, age, sex and BMI (SBP IHM-Control= −9.63 mmHg, 95% CI −14.28, −5.11, $p < 0.0001$). Figure 1 demonstrates results of ABPM and HBPM at the beginning and at the end of the study in the IHM group compared to the Control group.

The key finding of the present study is a statistically significant difference in the decrease in home BP between groups.

Discussion

The main finding of the present study is that home BP displayed at 6 months had a significantly greater reduction in IHM than in controls, whereas office did not. This emphasizes the superiority of HBPM over office BP measurements in detecting different BP effects induced by different management strategies.

The primary function of our cardiovascular system (CV) system is not a generation of BP but a delivery of oxygen to all tissues. BP is a measurable end product of an exceedingly complex series of factors, including those that control blood vessel caliber and responsiveness, those, which control fluid volume within and outside the vascular bed, and those, which control cardiac output. Data suggest that there is a strong relation between hypertension and abnormal hemodynamic modulators. In our previous paper we have demonstrated, that almost all (98.5%) uncontrolled hypertensive patients in the ESH Excellence centers presented at least one altered hemodynamic modulator: intravascular hypervolemia (96.4%) and/or hypoinotropy (42.5%) and/or vasoconstriction (49.3%) [1].

Because BP elevation is commonly treated like a symptom, without paying attention to the hemodynamic causes, physicians often neglect the other hemodynamic parameters like cardiac output, left ventricle contractility, and vascular resistance. It is all the more surprising since antihypertensive drugs modify the entire hemodynamic status. This could be an explanation for the relatively low rate of BP control in the hypertensive population.

In the current analysis of the BEAUTY study, we focused on home BP measurement in response to either drug selection algorithm according to non-invasive hemodynamic monitoring or conventional use of drugs in the Control group. The advantages of home BP monitoring in the management of treated

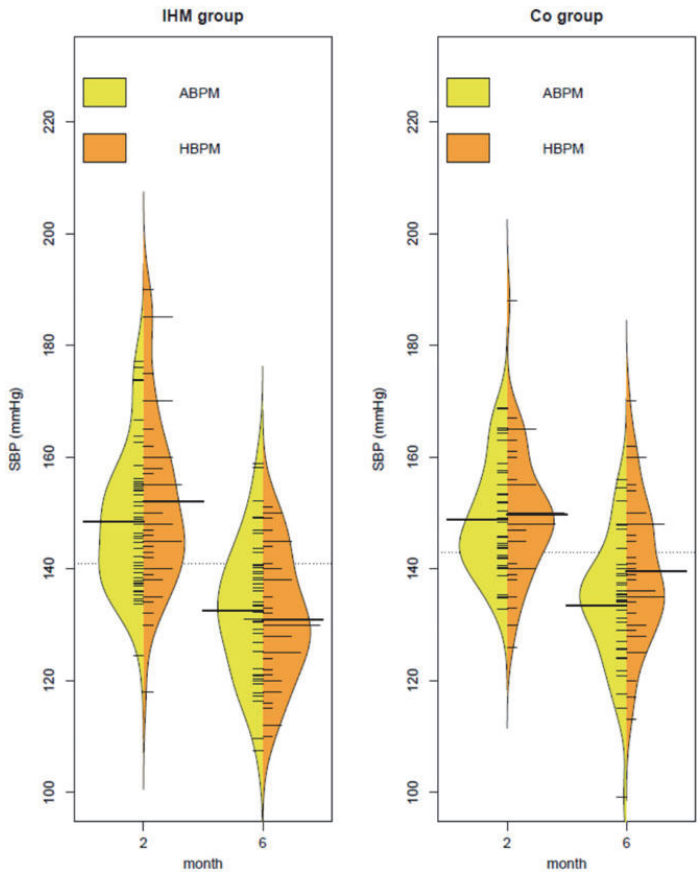

Figure 1. Comparison of home and ambulatory BP in the two groups.

hypertensive patients have been reported in many studies [16,17]. During the last years, guidelines have placed much greater emphasis on the utilization of out-of-office measurements including home BP measurements [8,10,11]. Home BP measurement has been demonstrated to be concordant with ambulatory blood pressure monitoring. Paolasso et al. reported no significant differences in the measurement of diurnal SBP and DBP between both methods [12]. Home BP values are obtained under stable conditions and can eliminate the white coat effect [13]. Use of home BP monitoring according to ESH guidelines, i.e. by considering the average of duplicate readings taken over a week before each office visit, after discarding the values measured during the first day (Parati et al. J Hypertens. 2008) yields highly reproducible values which are particularly appropriate for the management of hypertensive patients receiving antihypertensive drugs [13].

In the present study we have used validated home BP devices based on the same software as the devices used for 24h ABPM, i.e. the Microlife Watch-BP device, which also offered the possibility to perform and store home BP measurements following the 2008 ESH home BPM guidelines.

Our findings are in line with the evidence supporting the use of out-of-office monitoring in all aspects of routine clinical care, which has increased substantially in recent years and is reflected in an increased utilization of home BP monitoring by patients and clinicians [14]. Home BP self-measurement and monitoring improves patient's awareness and their adherence to prescribed treatment, thus favoring a better management of hypertension. This represents an important complementary support to the doctor-patient relationship in the office, with a high potential for improving hypertension management [15,16].

In our previous paper we have found no statistically significant difference between the decrease in office BP in IHM group compared to Control group [6]. We did not find either a significant difference in BP changes between groups when using ABPM, and these findings were replicated in the present subanalysis. In contrast, the key finding of the present study is the occurrence of a statistically significant difference in the decrease in home BP between groups. The reason for these discrepancies is not clear. We hypothesize that this finding might depend on specific features of home BP measurements which could make it best BP measurement method for drug trials or intervention studies. Home BP monitoring provides more reproducible data on an individual's BP; obtained at rest, repeated daily, and eliminating white coat effect. Moreover, home BP is more similar to «basal» blood pressure. The conclusion we can draw from our data is that home BP is more sensitive to drug selection algorithm in response to non-invasive hemodynamic monitoring than office and ABPM in patients with uncontrolled hypertension.

Study limitations

The present study must be interpreted within the context of the potential limitations. First, home BP measurements were not done in all BEAUTY study patients due to shortage of devices in some centers. Second, home BP monitoring was performed in 4 study centers out of five, home BP being a secondary endpoint and thus not obligatory according to the study protocol. However, in spite of these limitations, we have found a statistically significant greater reduction in home systolic blood pressure using IHM than in the control group. Further research is required in larger cohorts of patients, but our data clearly support the importance of out-of-office BP monitoring is in hypertension management.

Conclusions

In conclusion, easy-to-do non-invasive hemodynamic monitoring associated with a drug selection algorithm induced larger reduction in home BP compared to conventional drug selection in uncontrolled hypertensive patients referred to ESH Excellence Centers. Home BP monitoring appears to be a convenient method for BP measurement in clinical trials. These exploratory data should stimulate further studies aimed at investigating IHM-guided hypertension management in a larger number of subjects followed up not in excellence centers for hypertension but rather in in daily practice.

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Disclosure statement

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Curriculum vitae

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Education

Period	Organization	Position
2015–	Tallinn University of Technology	Doctoral studies (health care technology)
2000–2002	Estonian Neijing School	Chinese traditional medicine
1996–1998	Tartu University	Specialty program for family physicians, diploma
1994	Tartu University	MD exams for working in Estonia, and diploma (equal to Master's Degree)
1994–1995	Hospitals in Tallinn	Internship
1990–1993	Tampere University, Kuopio University	Faculty of Medicine, program in Medicine
1987–1990	Tartu University	Faculty of Medicine, program in Medicine
1976–1987	Tallinn Secondary School No 32	

Language competence

Estonian	Native speaker
English	Proficient speaker
Russian	Proficient speaker
Finnish	Fluent speaker
German	Basic skills

Professional employment

Period	Organization	Position
1996–	Medical Center "Sinu Arst"	Family Physician and Managing Director
2015–2017	Confido Private Medical Center	Family Physician
1992–1993	Kauhava (Finland) Medical Center	General Practitioner
1991–1992	Tornio (Finland) Psychiatric Hospital	General Practitioner
1986–1987	Tallinn Emergency Hospital	Care assistant in cardiac surgery unit

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Hariduskäik

Aeg	Asutus	Eriala
2015–	Tallinna Tehnikaülikool	tervisetehnoloogia doktoriõpe
2000–2002	Eesti Neijingi kool	Hiina traditsiooniline meditsiin
1996–1998	Tartu Ülikool	perearsti eriala, diplom
1994	Tartu Ülikool	arstilitsentsi eksamid töötamiseks Eestis; diplom (võrdsustatud magistrikraadiga)
1994– 995	Tallinna haiglad	internatuur
1990–1993	Tampere Ülikool, Kuopio Ülikool	arstiteaduskond, ravi eriala
1987–1990	Tartu Ülikool	arstiteaduskond
1976–1987	Tallinna 32. Keskkool	

Keelteoskus

Eesti keel	emakeel
Inglise keel	kesktase
Vene keel	kesktase
Soome keel	kõrgtase
Saksa keel	algtase

Teenistuskäik

Aeg	Asutus	Töökoht
1996–	Tervisekeskus Sinu Arst	perearst ja juhataja
2015–2017	Confido Erameditsiini Keskus	peremeditsiini eriarst
1992–1993	Kauhava (Soome) perearstikeskus	üldarst
1991–1992	Tornio (Soome) psühhiaatriahaigla	üldarst
1986–1987	Tallinna Kiirabihaigla	kardiokirurgia osakonna sanitar