Original Article

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Hemodynamic profiles in treatment-naive arterial hypertension and their clinical implication for treatment choice: an exploratory post hoc analysis

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Objective: Noninvasive thoracic bioimpedance by the HOTMAN System estimates hemodynamic modulators and expresses them as hemodynamic profiles. Aims of this analysis were to describe hemodynamic profiles among treatment-naive hypertensive patients compared with normotensive controls and to investigate whether a hemodynamic-guided choice of therapy improves blood pressure (BP) control within 4 weeks.

Method: This exploratory post hoc analysis used data of a randomized parallel-group trial including 80 outpatients with newly diagnosed arterial hypertension (AHT), randomized to four antihypertensive first-line monotherapies, and 20 age-matched and sex-matched normotensive controls. Hemodynamic profiles were measured at baseline and after four weeks of treatment. On the basis of the hemodynamic profiles, the most appropriate pharmacological treatment was determined retrospectively and patients were categorised to have received concordant (ConTG) or discordant treatment (DisTG).

Results: In the hypertensive group, hypervolemia with vasoconstriction was the predominant hemodynamic profile in 48% of patients and hypervolemia without vasoconstriction in 45%, compared with 15 and 50%, respectively, in the control group. After 4 weeks of treatment, the mean (±SD) 24-h BP was 129.9 (±11.0)/81.5 (±8.0) mmHg in the DisTG vs. 133.9 (±12.3)/84.0 (±9.1) mmHg in the ConTG ($P = 0.158/0.222$). The mean 24-h BP reductions were −9.7 (±10.1)/−5.0 (±6.2) mmHg in the DisTG and −12.4 (±14.8)/−6.9(±6.9) mmHg in the ConTG ($P = 0.353/0.223$). After 4 weeks of treatment, the BP control rate was 53.7% (43/80) among all, 55.7% (29/52) in the DisTG and 48% (12/25) in the ConTG ($P = 0.628$).

Conclusion: Our findings do not support the hypothesis that personalized treatment initiation based on hemodynamic profiles improves BP control in newly diagnosed hypertensive outpatients.

Keywords: antihypertensive therapy, hemodynamic profiles, HOTMAN system, hypertension

Abbreviations: ABPM, 24-h ambulatory blood pressure monitoring; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; BP, blood pressure; CCB, calcium-channel blocker; CI, cardiac index; ConTG, concordant treatment group; DisTG, discordant treatment group; EPCI, ejection phase contractility index; ESH, European Society of Hypertension; HCT, hydrochlorothiazide; HOTMAN, Hemodynamic and Oxygen Transport Monitoring & Management Systems; HR, heart rate; ICG, impedance cardiography; IQR, interquartile range; ISI, inotropic state index; LSWI, left stroke work index; MAP, mean arterial pressure; OBP, office blood pressure; PWA, pulse wave analysis; RAAS, renin—angiotensin–aldosterone system; RCT, randomized controlled trial; SD, standard deviation; SI, stroke index; SSVRI, stroke systemic vascular resistance index; TEB, thoracic electrical bioimpedance; TFC, thoracic fluid conductivity

INTRODUCTION

Arterial hypertension is a worldwide highly prevalent chronic disease [1]. Achieving blood pressure (BP) control is a challenge in everyday clinical practice, which is tackled by various strategies including different combinations of drugs [2]. Despite this, BP control rates have remained poor worldwide. As shown in previous studies, only ∼40% of patients with hypertension worldwide are treated and only 35% of these patients have a controlled BP of less than 140/90 mmHg [3]. This failure to achieve BP control in most hypertensive patients shows that we need new approaches to improve treatment especially

Journal of Hypertension 2021, 38:000–000

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Received 6 October 2020 **Revised** 29 November 2020 **Accepted** 29 November 2020

DOI:10.1097/HJH.0000000000002766

considering the increasingly tighter BP goals [4]. One approach, favored in recent guidelines, is to start empiric combination drug therapy to achieve rapid BP control, which is reasonable on a population level but may disregard the complex pathophysiology of hypertension in the individual patient [4,5]. An alternative approach might be to individually tailor therapy based on hemodynamic parameters.

Physiologically, BP is determined by intravascular volume, cardiac output, and peripheral vascular resistance [6,7]. Alterations of these hemodynamic modulators or a disbalance thereof lead to elevated blood pressure [8]. These hemodynamic modulators can be measured noninvasively by thoracic electrical bioimpedance (TEB). TEB was first used in the 1960s to measure noninvasively cardiac output in astronauts [9]. In brief, cardiac output is estimated by changes in thoracic bioimpedance based on the assumption that electric current will mainly travel along large vessels, that is, the thoracic aorta and the inferior and superior venae cavae through the thorax. Changes in aortic diameter during systole and diastole alter these currents, and therefore, TEB. By the use of mathematical algorithms, these alterations in TEB can then be used to estimate cardiac output [10,11]. In addition, various cardiodynamic and hemodynamic parameters can be derived by entering the present BP. Noninvasive measurement systems using bioimpedance have been used in previous studies to determine/monitor cardiac output [12]. One low-current TEB device, the HOTMAN System (Hemodynamic and Oxygen Transport Monitoring & Management Systems, Hemosapiens Medical Inc., Sedona, Arizona, USA) may have the advantage against older devices that it uses a very low current with digital data signal processing and improved mathematical algorithms [13]. Additionally, the systems report not only an estimation of the cardiac output and other hemodynamic modulators but also generates a hemodynamic profile expressed as hemodynamic map showing deviations of volemia, inotropy, chronotropy, and vasoactivity from their normal range (Supplementary digital Figure 1, http://links.lww.com/HJH/B545) [10]. The HOTMAN System has been validated against invasive measurement (thermodilution method) of the cardiac index (CI) [13] and has been used in previous studies, for example, to assess hemodynamic patterns in patients with various forms of hypertension, in obese patients [14], or to guide treatment decisions in patients with resistant or uncontrolled hypertension [15–17].

Aim of this study was to describe hemodynamic profiles among newly diagnosed hypertensive patients compared with normotensive control patients and to investigate whether a hemodynamic-guided personalized drug treatment improves BP control within 4 weeks.

METHODS

This is an exploratory post hoc analysis of a randomized, open-label, parallel-group study in patients with treatment-naive arterial hypertension. The study was investigating renin–angiotensin–aldosterone peptide concentrations and noninvasive hemodynamic measurements at baseline and 4 weeks after initiation of first-line antihypertensive treatment. The trial was conducted at the Hypertension Clinic of the Medical Outpatient Department of the University Hospital Basel, Switzerland from April 2015 to March 2018.

Patient selection

Eighty patients newly diagnosed with primary arterial hypertension requiring antihypertensive drug treatment were randomized in a 1 : 1 : 1 : 1 ratio to one out of four first-line guidelines-recommended treatment groups [18]: angiotensin-converting enzyme inhibitor (ACEi): perindopril 5 mg; angiotensin receptor blocker (ARB): olmesartan 20 mg; calcium-channel blocker (CCB): amlodipin 5 mg; or hydrochlothiazide (HCT): hydrochlorothiazide 25 mg.

Full inclusion and exclusion criteria can be found in Supplementary digital Table 1, http://links.lww.com/HJH/B547. In brief, patients had to be at least 18 years of age and newly diagnosed with primary grade I or II arterial hypertension, confirmed by 24-h ambulatory blood pressure monitoring (ABPM) and previously untreated. Diagnostic work-up to exclude secondary forms of hypertension has been done according to the 2013 European Society of Hypertension (ESH) guidelines [18].

Control group

Twenty age-matched and sex-matched healthy and normotensive participants were included as control group with recruitment in a 4 : 1 fashion. Normotension was confirmed by ABPM according to the cut-off values of mean 24-h, awake and asleep BP as defined by the 2013 ESH guidelines [18].

Trial registration

The trial protocol was approved by local ethics committee (Ethikkommission Nordwest- und Zentralschweiz EKNZ 2015-081). The study has been registered in the US trial registry (clinicaltrials.gov, NCT02449811) and was performed in accordance with the Declaration of Helsinki and its amendments, International Conference on Harmonization, Good Clinical Practice guidelines, and applicable national laws and regulations. Anonymized data supporting the findings of this study are available from the corresponding author upon reasonable request.

Study procedure

An overview of the study procedure is shown in Fig. 1. Patients with primary arterial hypertension confirmed by ABPM were included into the intervention group.

At baseline, blood tests, office blood pressure (OBP) measurements, noninvasive hemodynamic measurements using the thoracic bioimpedance device (HOTMAN System, Hemo Sapiens Medical Inc., Sedona, Arizona, USA) and randomization were performed by a study nurse in all patients. After completion of the measurements, patients were randomized to one of the four treatment groups, treating physicians were blinded for the results of the hemodynamic measurements. After 4 weeks of treatment, ABPM, OBP, and hemodynamic measurements were

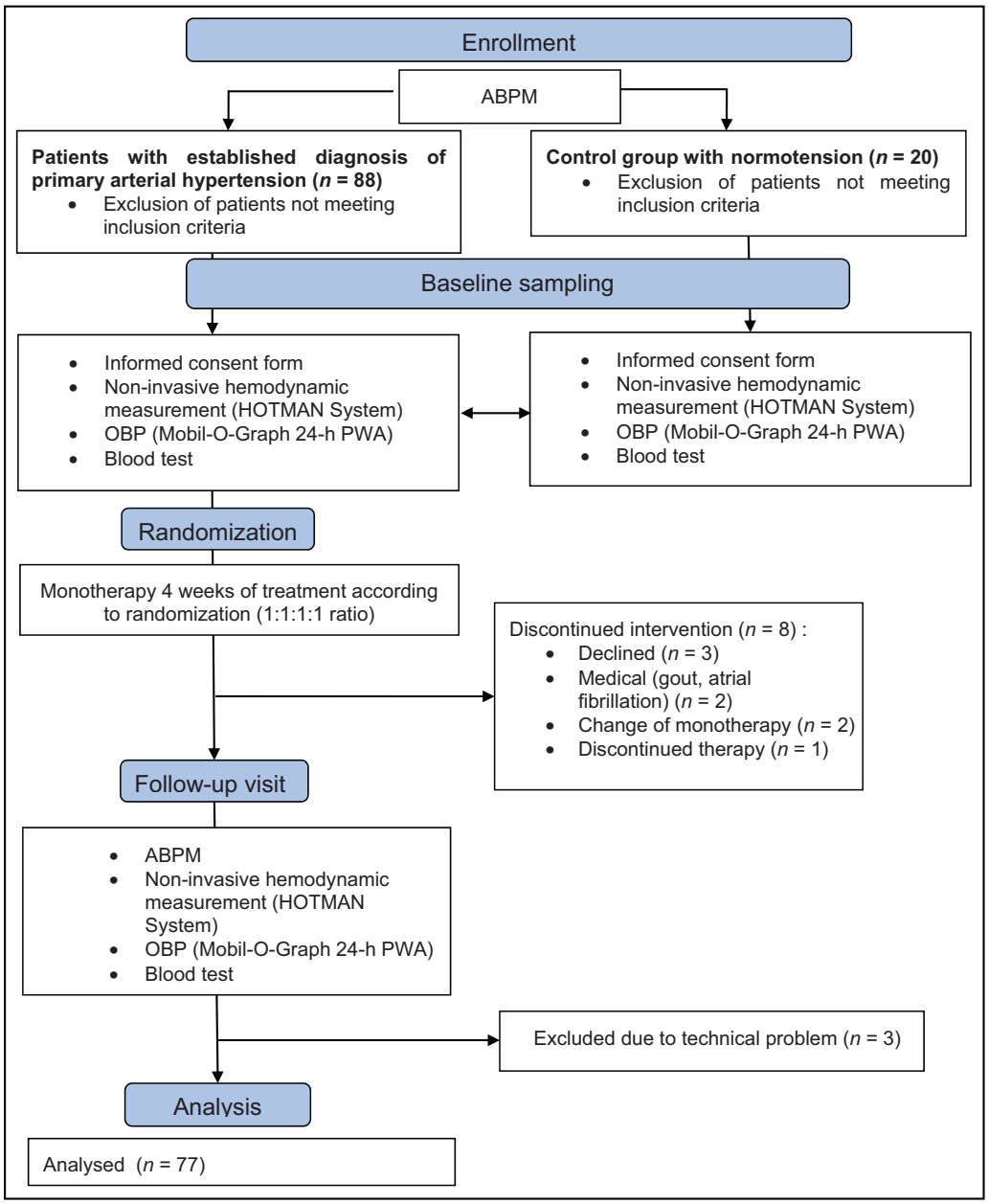

FIGURE 1 Overview about the study procedure. ABPM: ambulatory blood pressure measurement; OBP office blood pressure measurement, PWA: pulse wave analysis.

repeated. Hemodynamic measurements were taken in supine position with two pairs of electrodes positioned on the upper neck and upper abdomen (giving current) and two pairs of electrodes at the base of the neck and the diaphragm level (measurement). After 5 min of rest, three consecutive hemodynamic measurements spaced 2 min apart were recorded together with OBP measurements performed with a Mobil-O-Graph 24-h PWA (pulse wave analysis) monitor (IEM) [19].

Hemodynamic data

Of the three hemodynamic measurements, the last one with the best signal quality (regularity of the pulse curves, artefact load) was used for analysis. Alterations in the thoracic impedance were analyzed by the HOTMAN system providing hemodynamic parameters related to blood flow [cardiac index (CI)], hemodynamic state [stroke index (SI)], the heart rate (HR), the afterload [stroke systemic vascular resistance index (SSVRI)], the inotropy [inotropic state index (ISI)], the left ventricular contractility [left stroke work index (LSWI), ejection phase contractility index (EPCI)] and thoracic fluid conductivity (TFC). The inotropic state index (ISI) and left stroke work index (LSWI), were used to estimate the intravascular volume according to the Frank–Starling Law and indicated as quotient of the values (LSWI/ISI) [20].

The system also generated a graph showing the patient's hemodynamic status (i.e. their hemodynamic profile) in a hemodynamic map marking the deviations (in +/-%) of volemia, inotropy, vasoactivity, and chronotropy from their normal range (a function of age, sex, and clinical state) as exemplary shown in Supplementary digital Figure 1, http://links.lww.com/HJH/B545 [10].

Blood pressure measurements

The mean of the second and third BP measurement was determined as OBP. ABPM was repeated after 4 weeks of treatment. The awake and asleep time was taken from patient's protocol. According to the ABPM, patients were categorized as having or having not reached BP targets according to the 2013 ESH guidelines for management of arterial hypertension [18]. Controlled blood pressure was defined as mean 24-h, awake and asleep BP values within normal ranges defined by the 2013 ESH guidelines, namely less than 130/80 mmHg, less than 135/85 mmHg, and less than 120/70 mmHg.

Control group

A control group of 20 age-matched and gender-matched, healthy and normotensive participants were recruited to examine the hemodynamic characteristics at baseline in a normotensive population. After having provided written informed consent, normotension was documented with ABPM. In this normotensive control group, OBP measurements and hemodynamic measurements with the HOTMAN device were taken at a baseline visit.

Allocation to concordant or discordant treatment group

To investigate whether hemodynamic-guided choice of antihypertensive therapy may improve BP control, three hypertension experts retrospectively reviewed hemodynamic measurements. Therefore, the experts followed the following steps:

At first, the system-generated hemodynamic profiles were subclassified in main hemodynamic pattern subgroups according to the percent-deviations of volemia, inotropy, vasoactivity, and chronotropy: hypervolemia without vasoconstriction pattern, hypervolemia with vasoconstriction (mixed) pattern and vasoconstriction without hypervolemia pattern group.

In a second step, baseline system-generated hemodynamic maps of each patient were reviewed by all three experts separately. They determined independently the most appropriate treatment according to the individual hemodynamic situation and the anticipated pharmacological effects of the antihypertensive drugs (e.g. HCT for patients with hypervolemia without vasoconstriction, ACEi or ARB for mixed profiles with vasoconstriction and hypervolemia, or CCB for profiles with predominant vasoconstriction). To reduce bias, they were blinded about patient characteristics, assigned treatment and treatment effect after 4 weeks. After independent judgement, evaluation was compared and the majority response was determined as treatment of choice. This result was compared to the allocated treatment and patients thus categorized as having received concordant (ConTG) or discordant (DisTG) treatment. As example, in a patient with hypervolemia without vasoconstriction, the most appropriate treatment was judged to be HCT. If this patient was randomized to HCT, he was categorized in the concordant treatment group (ConTG), but if he was randomized to a ACEi, ARB, or CCB, he was then categorized in the discordant treatment group (DisTG).

Statistical methodology

Findings were descriptively presented in graphs. Normal distribution was assessed (Shapiro–Wilk W test), normally distributed results were summarized in means and standard deviation, not-normally distributed results were summarized in medians and its interquartile ranges. Normally distributed values were compared with independent sample t test analysis and the not-normally distributed were analysed with the Mann–Whitney U test, using IBM SPSS Statistics Version 22 (IBM, Armonk, New York, USA). The Violin plots graphs were done using R, Version 3.6.0 (R Foundation, Vienna, Austria). Dichotomous variables were given as absolute numbers in percentage and compared with the Fisher's exact test. P value less than 0.05 was defined as statistical significant.

RESULTS

Baseline characteristics

Baseline characteristics of the hypertensive and the control group are displayed in Table 1. In the hypertensive group, median (IQR) age, BMI, and gender proportion were 48.6 (36.1–59) years, 26.5 (23.8–29.0) kg/m^2, and 74% men, respectively, at baseline. The median age and gender proportion in the hypertensive group differed not significantly in the control group [50.2 (37.8–60.4) years, $P = 0.816$ and 70% men, $P = 0.737$, respectively]. The BMI was significantly higher in the hypertensive group than in the control group [26.5 (23.8–29.0) vs. 22.2 (21.1–24.7) kg/m^2, respectively, $P < 0.0005$].

The median 24-h SBP/DBP by ABPM was 139.0 (135.0–148.0)/89.0 (82.0–94.0) mmHg among the hypertensive group compared with 121 (113.5–124.8)/76 (70.0–77.8) mmHg ($P < 0.0005/<0.0005$) in the control group. The LSWI/ISI and SSVRI were statistically significantly higher among the hypertensive group compared with the control group [LSWI/ISI 71.0 (63.4–79.3) vs. 62.2 (55.2–64.2), $P < 0.0005$ and SSVRI 188.9 (145.9–249.2) vs. 147.5 (108.2–192.6), $P = 0.004$]. There was no statistically significant difference for the other hemodynamic values between the two groups. Further blood pressure results and the main hemodynamic values are summarized in Table 1.

System-generated hemodynamic profiles at baseline

At baseline, the system-generated hemodynamic profiles were rated as normal in 10% of the control group and in 1% of the hypertensive group. In the hypertensive group, hypervolemia with vasoconstriction (mixed) was the predominant hemodynamic profile in 48% and hypervolemia

TABLE 1. Characteristics at baseline among hypertensive and control group

	Hypertensive group ($N = 80$)	Control group ($N = 20$)	P value[b]
Sex, *N* male (%)/total	59 (73.8%)/80	14 (70.0%)/20	0.737
Age (years)	48.6 (36.1–59.0)	50.2 (37.8–60.4)	0.816
Height (m)	1.75 (1.69–1.81)	1.77 (1.69–1.82)	0.560
Weight (kg)	81.0 (71.0–89.0)	74.0 (64.5–77.0)	0.016
BMI (kg/m^2)	26.5 (23.8–29.0)	22.2 (21.1–24.7)	<0.0005
24-h HR	75.0 (69.0–82.0)	66.5 (65.0–74.5)	0.009
24-h SBP/DBP	139.0 (135.0–148.0)/89.0 (82.0–94.0)	121 (113.5–124.8)/76 (70.0–77.8)	<0.0005/<0.0005
Awake SBP/DBP	145 (140.0–151.0)/92 (87.0–99.0)	124.5 (116.8–128.8)/78.5 (73.3–82.0)	<0.0005/<0.0005
Asleep SBP/DBP	126.0 (119.0–136.0)/78.0 (69.0–83.0)	108.0 (99.3–112.0)/63.5 (58.3–67.8)	<0.0005/<0.0005
sOBP/dOBP	139.5 (131.5–147.5)/90.0 (83.5–97.5)	126.0 (111.8–131.3)/78.0 (74.0–80.0)	<0.0005/<0.0005
CI (l/min per m^2)	3.0 (2.2–3.5)[a]	3.0 (2.5–3.7)	0.414
SI (ml/m^2)	43.0 (32.0–55.0)[a]	48.0 (38.0–70.5)	0.152
ISI (s$^{-1)}$	0.9 (0.69–1.1)[a]	1.0 (0.79–1.35)	0.075
LSWI (g.m/m^2)	61.1 (47.3–81.0)[a]	57.3 (41.5–84.7)	0.855
LSWI/ISI	71.0 (63.4–79.3)[a]	62.2 (55.2–64.2)	<0.0005
SSVRI (FΩ)	188.9 (145.9–249.2)[a]	147.5 (108.2–192.6)	0.004
TFC (Ω^{-1})	0.03 (0.03–0.03)[a]	0.03 (0.03–0.03)	0.469
EPCI (s^{-1})	0.04 (0.03–0.05)[a]	0.04 (0.04–0.06)	0.084

Variables are expressed as median (IQR). CI, cardiac index; dOBP, diastolic office blood pressure; EPCI, ejection phase contractility index; HR, heart rate; ISI, inotropic state index; LSWI, left stroke work index; SI, stroke index; sOBP, systolic office blood pressure; SSVRI, stroke systemic vascular resistance index; TFC, thoracic fluid conductivity.
[a]$N = 77$ hypertensive group.
[b]Mann –Whitney *U* test.

without vasoconstriction in 45%, whereas in the control group, 50% showed a profile of hypervolemia without vasoconstriction, 15% hypervolemia with vasoconstriction (mixed), and 15% vasoconstriction without hypervolemia (Fig. 2).

As previously described in the methods, the HOTMAN system provides deviations from normal range of the main hemodynamic parameters: volemia, inotropy, vasoactivity, and chronotropy. Supplementary digital Figure 2, http://links.lww.com/HJH/B546 shows the distribution of these deviations (in percentage) in the hypertensive group and in the control group. It shows that the percentage-deviation of hypervolemia from normal range is higher among the hypertensive group than in the normal group. The percentage-deviation of vasoconstriction is also higher among the hypertensive group compared with the control group. Figure 2 and Supplementary digital Figure 2, http://links.lww.com/HJH/B546 also show that the distribution of these parameters among the control group are not mainly in the 'normal' range and that normotension does not equal to normovolemia.

Randomization to treatment

In the DisTG, 44.2% received either ACEi or ARB (RAASi Group), 36.5% CCB and 19.2% HCT (52 patients in total). In the ConTG, (25 patients in total), 64% received ACEi or ARB (RAASi Group), 8% CCB, and 28% HCT.

Analysis of blood pressure measurements at baseline

At baseline, the mean (±SD) 24-h BP was 139.4 (±7.5)/86.4 (±7.3) mmHg in the DisTG and 146.3 (±10.4)/91.0 (±7.9) mmHg in the ConTG ($P = 0.001/0.015$). The mean awake BP was 145.0 (±7.9)/90.6 (±7.6) mmHg in the DisTG and 150.4 (±9.9)/94.7 (±8.3) mmHg in the ConTG ($P = 0.011/0.034$). ABPM and OBP values at baseline and after 4 weeks of treatment including BP response in the DisTG and the

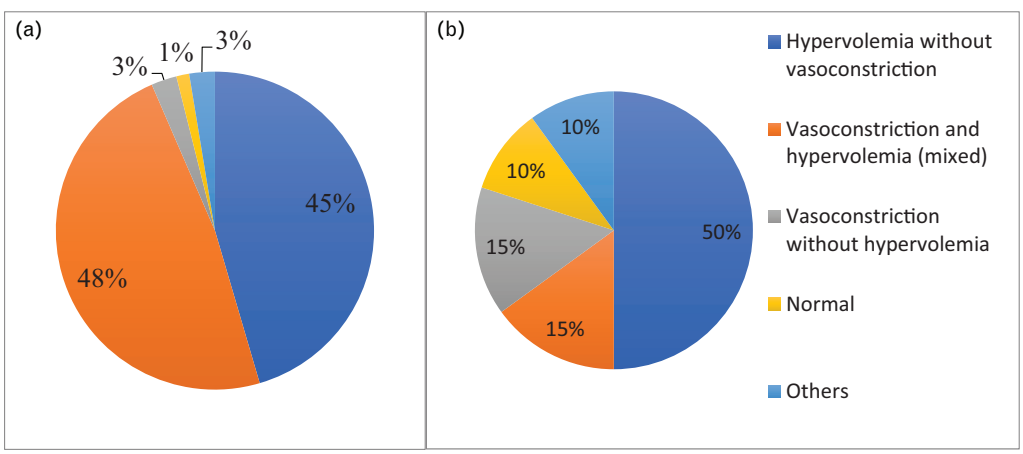

FIGURE 2 Hemodynamic profiles at baseline among treatment-naive hypertensive patients. (a) (N = 77) and control group (b) (N = 20).

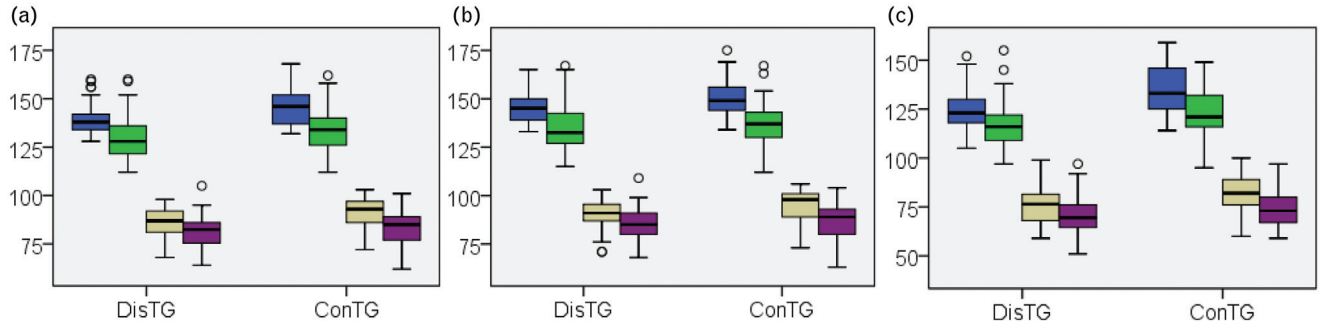

FIGURE 3 Ambulatory blood pressure monitoring at baseline and after 4 weeks of treatment, among discordant treatment group and concordant treatment group. (a) 24-h SBP/DBP; (b) awake SBP/DB; (c) asleep SBP/DBP. Blue box, SBP at baseline; green, SBP after 4 weeks; beige, DBP at baseline; violet, DBP after 4 weeks. X-axis, DisTG and ConTG; Y axis, BP in mmHg.

ConTG are summarized in Supplementary digital Table 2, http://links.lww.com/HJH/B548.

Analysis of blood pressure measurements after 4 weeks of treatment

After 4 weeks of treatment, the mean (±SD) 24-h BP was 129.9 (±11.0)/81.5 (±8.0) mmHg in the DisTG vs. 133.9 (±12.3)/84.0 (±9.1) mmHg in the ConTG ($P = 0.158/0.222$). The mean awake BP was 134.5 (±11.5)/85.5 (±8.3) mmHg in the DisTG and 137.6 (±12.8)/87.2 (±9) mmHg in the ConTG ($P = 0.294/0.428$). The 24-h, awake and asleep BP measurements after 4 weeks of treatment among the ConTG and DisTG are shown in Fig. 3. ABPM and OBP values at baseline and after 4 weeks of treatment including BP response in the DisTG and the ConTG are summarized in Supplementary digital Table 2, http://links.lww.com/HJH/B548.

The mean 24-h BP reductions were −9.7 (±10.1)/−5.0 (±6.2) mmHg in the DisTG and −12.4 (±14.8)/−6.9 (±6.9) mmHg in the ConTG ($P = 0.353/0.223$), meaning a SBP/DBP reduction of 7%/5.8% in the DisTG and 8.5%/7.6% in the ConTG. The mean BP reductions after 4 weeks of treatment are shown in Fig. 4.

Blood pressure control rate after 4 weeks of treatment

After 4 weeks of treatment, the BP control rate was 53.7% (43/80) among all, 55.7% (29/52) in the DisTG and 48% (12/25) in the ConTG ($P = 0.6275$ DisTG vs. ConTG, Fisher's Test).

DISCUSSION

Our study showed that in patients with treatment-naive hypertension, the predominant hemodynamic profiles at baseline were hypervolemia without vasoconstriction and hypervolemia with vasoconstriction (mixed). Hypervolemia was clearly the predominant component in the hemodynamic profiles (93%) among hypertensive but otherwise asymptomatic patients (without clinical signs of volume overload). The predominance of these mixed profiles (hypervolemia and vasoconstriction) and of hypervolemia as single modulator have also been shown in a previous study among uncontrolled hypertensive patients also using the HOTMAN System [8].

Interestingly, only 10% of normotensive control patients in our analysis showed a normal system-generated hemodynamic profile with all modulators within normal range. The predominant hemodynamic profile among the control group was a mixed pattern of hypervolemia with vasoconstriction. Regarding single modulators, hypervolemia was again the most prevalent – but compared with the hypertensive group the degree of the deviation from normal range was lower.

Reasons for these observations may be: firstly, calculated values of the HOTMAN System can be biased. These calculations are based on a physiologic model with ideal stroke index (SI) and mean arterial pressure (MAP) range and the hemodynamic profiling is related to the accuracy of the measurements namely the thoracic bioimpedance and the noninvasive blood pressure. Their accuracy can be

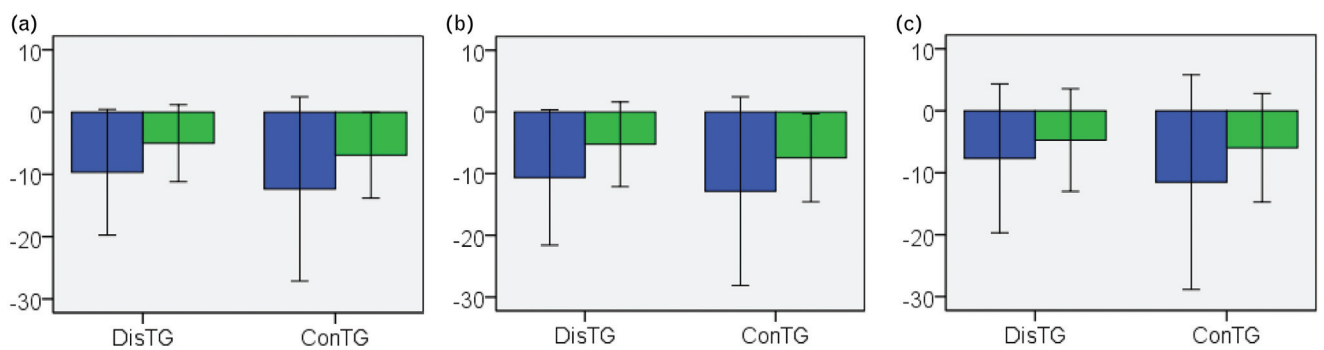

FIGURE 4 Mean blood pressure reduction in mmHg after 4 weeks of treatment (a) 24-h SBP/DBP; (b) awake SBP/DBP; (c) asleep SBP/DBP. Blue box: mean reduction of SBP; green, mean reduction of DBP. X axis, DisTG and ConTG; Y axis, mmHg.

altered depending on the clinical conditions of the measurement [10]. Therefore, the interpretation of the 'normal' or 'not normal' hemodynamic profile should be used cautiously and only under consideration of the clinical state of the patient. Secondly, we assume that hemodynamics are a continuum with the possibility of dysregulation of one hemodynamic modulator and counter-regulation by another. Therefore, a normotensive status does not necessarily correspond to a hemodynamic profile within the normal range. BP can be seen as continuum, too, with arbitrary defined ranges and cut-off values. Therefore, not hypertensive individuals can be subdivided into optimal, normal, or prehypertensive with beginning hemodynamic alterations [4]. As consequence, in our analysis, deviation from a normal state were more pronounced in the hypertensive group than in the control group.

Additionally, we investigated whether an individualized approach of hemodynamic-guided therapy could have the potential to improve BP control within 4 weeks. Theoretically, a tailored therapy based on the hemodynamic alterations, and thus the individual pathophysiology should provide a more effective BP reduction. Though the 24-h BP reduction was more pronounced in the ConTG compared with the DisTG with a SBP/DBP reduction of −12.4 (±14.8)/−6.9 (±6.9) mmHg vs. −9.7 (±10.1)/−5.0 (±6.2) mmHg, the differences were not statistically significant. Additionally, the control rate after 4 weeks was not higher in the ConTG group.

Consequently, we found no advantage of a personalized monotherapy over discordant monotherapy.

This may have several reasons: the average SBP at baseline was, by chance, significantly (7 mmHg) lower in the DisTG than in the ConTG. This may lead to a more pronounced blood pressure reduction in the ConTG group because of the higher baseline BP values at therapy initiation, and a lower control rate in the ConTG group, as the DisTG group started closer to the BP targets. This effect is purely by chance, as the patients were randomly assigned to the four treatment groups and only post hoc labelled as ConTG or DisTG based on their hemodynamic profile. Keeping these points in mind, the difference in BP reduction may be even lower in a large randomized controlled trial (RCT) comparing ConTG to standard therapy with a more balanced baseline BP between both groups. When we consider that in our post hoc analysis, we decided dichotomously between a concordant treatment vs. a discordant treatment, and in a prospective intention-to-treat RCT, we would rather use a randomization to hemodynamically guided (concordant) vs. usual treatment, the treatment effect might even diminish, as in the usual treatment group, some patients will be treated concordantly by chance as well. At least, treatment effects are usually overestimated in studies with lower patient numbers than in larger randomized trials.

Our neutral results are consistent with the findings of the BEAUTY Study, which showed that noninvasive hemodynamic assessment combined with a drug selection algorithm did not result in a better reduction of daytime SBP in ambulatory BP monitoring among uncontrolled hypertensive patients [16]. The subanalysis of home BP measurements in the BEAUTY study; however, showed that the drug selection based on hemodynamic monitoring significantly improved home BP after 6 months compared with the control group ($P = 0.002$) [17]. Similarly, a randomized prospective controlled trial in 2016 using impedance cardiography (ICG)-guided antihypertensive therapy showed a greater BP reduction in the ICG-guided group among the patients with higher BP but did not significantly reduce BP among patients with slightly elevated BP [21].

Hemodynamics in arterial hypertension are complex, 'intrigate' each other, and cannot be resumed as four independent parameters. Lowering BP, for example, by vasodilation can lead to an activation of the RAAS system, and volume reduction can lead to a compensatory vasoconstriction. Other studies have shown that HCT raises angiotensin II, probably because of a decreased renal blood flow, which leads to an activation of the RAAS system [22].

Therefore, the lack of predictability of response to treatment based on noninvasive hemodynamics and the results of predominantly mixed hemodynamic profiles supports the recommendation of the current European Society of Cardiology (ESC)/ESH guidelines to initiate treatment as a combination of at least two active agents, which would be even more difficult to predict by noninvasive hemodynamics. Additionally, we observe only a control rate of 56% of patients after 4 weeks of monotherapy.

There were several limitations in this study. First, the post hoc analysis was made on a study focusing on changes in RAAS peptide profiles and hemodynamics after randomized treatment initiation. There was a disbalance in the number of patients in the ConTG and DisTG as well as differences in the baseline BP values. Retrospective allocation to the ConTG or DisTG was done by hypertension experts, however, we cannot exclude a bias in the process of the allocation. This allocation was done based on the results of the hemodynamic measurements with blinding for treatment, the other's results, as well as treatment effects.

To date, the noninvasive measures with the HOTMAN system are not a clinical standard, even if the device has been used in several trials.

The present analysis has several strengths: all hemodynamic and BP measures were performed under standardized conditions at the same center and a complete follow-up was achieved at 4 weeks. A 24-h BP measurement was used as both an inclusion criteria and as follow-up parameter. The parallel evaluation of the hemodynamic profiles by three experts might be not generalizable for a broader group but was on purpose clinically oriented and aimed to simulate the every-day decision-making when personalized hemodynamic profiles are available.

In conclusion, findings of the present analysis describe mainly mixed hemodynamic profiles with hypervolemia and vasoconstriction in patients with newly diagnosed hypertension. They do not support the hypothesis that personalized treatment initiation based on hemodynamic profiles improves BP control in comparison to randomized treatment assignment in newly diagnosed hypertensive outpatients.

ACKNOWLEDGEMENTS

We thank all participants of this study. The results of this exploratory post hoc analysis were presented as oral poster presentation at the 29th ESH European Meeting on

Hypertension and Cardiovascular Protection taking place from 21 June 2019 to 24 June 2019 in Milan, Italy.

Funding: The present study received funding from the Cardiovascular Research Foundation Basel and material support (electrodes for the measurements) from Hemo Sapiens Inc.

Conflicts of interest

O.P. reports personal fees from Novartis, Pfizer, MSD, Vifor Pharma and grants and personal fees from Boehringer Ingelheim, AstraZeneca, and grants from Sanofi and Bayer, outside the submitted work. T.B. reports personal fees from Servier, Amgen, Takeda, Menarini, MSD, Sanofi, and Vifor, outside the submitted work and material support (electrodes for the measurements) for the present study from Hemo Sapiens Inc. D.G., C.B., A.S.V., A.V., T.S., A.M., M.M. and M.H. have nothing to disclose.

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