Research Article

Management of Therapy Resistant Hypertension Guided by Non-Invasive Hemodynamic Measurements; an Observational Study -

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STRUCTURED ABSTRACT

Objective: Management of patients with therapy resistant hypertension is largely guided by empiricism and remains challenging. The study was designed to guide the medical therapy by thorax impedance derived hemodynamics in real-life out-patient office settings.

Methods: Fifty patients, 22 females, 61.8 ± 8.0 years of age and 28 males, 63.0 ± 12.0 years of age with confirmed therapy resistant hypertension were studied at baseline and 6 and 12 months follow-up. In each patient office and ambulatory 24 hours blood pressure measurements were taken at each data point. Antihypertensive medication was adjusted based on the outcome of hemodynamic measurements utilizing the HOTMAN-System® thoracic impedance. Specifically, the hemodynamic modulators Volume Status (VS), Vasotonus (VT) and Left Stroke Work Index (LSWI) were measured.

Results: At six months follow-up office and 24 hours ambulatory blood pressure measurements in patients' cohort significant reduction of systolic and diastolic pressures from baseline 170.3 ± 20.7/ 90.2 ± 13.3 mmHg to 149.26 ± 18.5/ 82.3 ± 13.2 mmHg ($p < 0.0001$/ $p < 0.0015$) and 144.4 ± 18.2/ 82.8 ± 12.6 mmHg to 130.1 ± 15.5/ 76.0 ± 12.8 mmHg ($p < 0.0001$ and $p < 0.0006$), respectively, was noted. On twelve months follow-up the positive effect was largely maintained but no further blood pressure reduction was achieved. Among the hemodynamic modulators hypervolumic state has been the most frequent (87.8%) and the most prominent (136. 0 ± 134.1%) factor. At six months follow-up volume state reduction to 73.7% ± 26.4% ($p = 0.002$) was achieved.

Conclusions: In patients with therapy resistant hypertension hemodynamically- guided blood pressure management may represent complementary approach to the current empiricism- guided means to improve blood pressure control.

CONDENSED ABSTRACT

To determine the efficacy of hemodynamic guidance in patients with Therapy Resistant Hypertension (TRH) we studied 50 patients 22 females, 61.8 ± 8.0 years of age and 28 males, 63.0 ± 12.0 years of age at baseline and six and twelve months follow- up using thoracic impedance to determine the hemodynamic modulators volume status, vasotonus and left stroke work index. After six months a significant reduction in the office and 24 hours ambulatory systolic and diastolic blood pressure was achieved. At twelve months follow-up no further blood pressure reduction was achieved. Hemodynamic guidance may be complementary to the current empiricism- based approach in patients TRH.

Keywords: Hypertension; Therapy Resistance; Hemodynamic Guidance; Medical Management

INTRODUCTION

Management of Therapy Resistant Hypertension (TRH) still represents a considerable medical challenge to both practitioners and specialists [1]. Based on current European guidelines TRH is defined as blood pressure >140/ 90mmHg despite of life style adjustments, administration of a full dose of a diuretic and optimal dose of at least two antihypertensive agents of different classes [2]. At present TRH management is largely based on expertise-based empiricism of individual physicians conducting the treatment. Using this approach TRH rates of up to 20% of treated cohorts appears realistic [3,16].

Alternatively to the traditional approach, therapy based on pathophysiology of TRH in individual patients could be considered, provided availability of means to assess the major blood pressure modulators by simple and non-invasive means. Recently, based on the principles of thoracic impedance device [4] non-invasive measurements of blood-pressure relevant hemodynamic parameters have become clinically available [4,5]. In an early multi-centric prospective randomized trial in patients with hypertension, but not TRH, no statistically relevant superiority of the pathophysiology- based over the standard empiricism- based approach was reported [5], possibly due to the already excellent management of these patients in the participating tertiary hypertension centers.

This study was designed to determine the efficacy of the individualized pathophysiology- guided management in patients with documented TRH in the real- life settings of an out- patient office in a non-randomized prospective model.

METHODS

Fifty patients treated for hypertension in the out-patient office of one of the authors (RaS) and with documented TRH were included in the study. Inclusion and exclusion criteria are given in table 1.

The study was approved by the Ethics committee of the chamber of physicians, Saxony – Anhalt; all patients signed informed consent.

Studies and evaluations performed at baseline, at six and 12 months follow up are summarized in table 2.

The hemodynamic modulators of blood pressure were the inotropic-, volume - and vasoactivity status of the patients. To determine these hemodynamic modulators HOTMAN˚-System designed to measure the thorax impedance was employed described elsewhere [4]. Briefly, the skin was prepared and 8 electrodes were placed in a standard fashion positioned at the left and right side of

Table 1: Inclusion and exclusion criteria for study participation.

Inclusion Criteria	Exclusion Criteria
• Patients with a mean office blood pressure > 140mmHg of systolic and > 90mmHg diastolic; ≥ 3 antihypertensive, two antihypertensive in sufficient dosage and one diuretic • Men and women aged > 18 and < 75 years • Signed written consent form	• Existence of an unstable disease • Life expectancy < 2 years

Table 2: Summary of clinical evaluations at baseline, six and 12 months follow-up

Clinical evaluations at baseline, six and 12 months follow-up
• Body Mass Index (BMI) • Office blood pressure • Mean blood pressure (Ambulatory Blood Pressure Monitoring) ABPM • Mean blood pressure (Day) ABPM • Mean blood pressure (Night) ABPM • Measurements of the hemodynamic modulators by HOTMAN®System: Volume State, Vasoacticity, Dynamicity

the neck and two electrodes on each side of the thorax and signal quality was controlled. To perform the measurements the patients were placed in recumbent position. Following 10 minutes of rest the blood pressure cuff was fastened on the upper arm (left or right upper arm, depending on the level of blood pressure; always the arm with the higher blood pressure was selected) and the pulse oximeter was attached to the tip of the second finger. Subsequently, in one minute intervals ten hemodynamic measurements and ten blood pressure measurements were taken and averaged. The hemodynamic measurements were automatically displayed on the rectangular matrix employing the vertical and horizontal axis for mean blood pressure and systemic impedance and diagonal co-ordinates system to display the hemodynamic modulators (Figure 1).

While, all patients received optimum medical treatment for TRH recommended by the current guidelines [2] all changes in medication were based on the outcome of the hemodynamic measurements; thus, in all patients the hemodynamic modulator with the highest deviation from the normal value was targeted.

All data were presented as average ± SD. Significance was assumed at the $p \leq 0.05$. Statistical significance was calculated using the pair-wise-one-way ANOVA repeated measure with Bonferroni's multiple comparison post-hoc test. All statistical calculations were performed using the GraphPad Prism 6 (GraphPad Software, San Diego, CA, USA).

RESULTS

50 patients 22 females, 61.8 ± 8.0 years of age and 28 males, 63.0 ± 12.0 years of age were included in the study.

Demographic data

Office blood pressure measurements revealed statistically significant reduction from baseline 170.30 ± 20.7/ 90.8 ± 13.3 mmHg to 149.26 ± 18.5/ 82.3 ± 13.2 mmHg ($p < 0.0001/ p < 0.0015$) at six months. Compared to the blood pressure measurements at six months no additional statistically significant reduction in blood pressure measurements at twelve months was observed (Figure 2).

Similarly, significant reduction in the mean 24 hours blood pressure with corresponding values of 144.4 ± 18.2/ 82.8 ± 12.6 mmHg at baseline and of 130.1 ± 15.5/ 76.2 ± 12.8 mmHg at six month follow-up was observed ($p = 0.0001/ p = 0.0006$). Compared to the blood pressure measurements at six months no additional statistically significant reduction in blood pressure measurements at twelve months was observed (Figure 3).

The impedance guided TRH monitoring led to a permanent decrease in mean blood pressure initially reached at the first follow-up interval of 6 months and kept stable for the remainder of the study.

Significant reduction in the mean blood pressure during the day with corresponding values of 146.3 ± 18.94/ 82.8 ± 12.6 mmHg at baseline and of 134.2 ± 16.6/ 78.2 ± 11.8 mmHg at six month follow-up was observed ($p = 0.0001/ p = 0.001$). Compared to the blood pressure measurements at six months no additional statistically significant reduction in blood pressure measurements at twelve months was observed (Figure 4).

Significant reduction in the mean blood pressure during the night with corresponding values of 140.1 ± 17.9/ 81.5 ± 14.7 mmHg at baseline and of 125.7 ± 16.8/ 71.3 ± 12.2 mmHg at six month follow-up was observed ($p = 0.0001/ p = 0.0001$). Compared to the
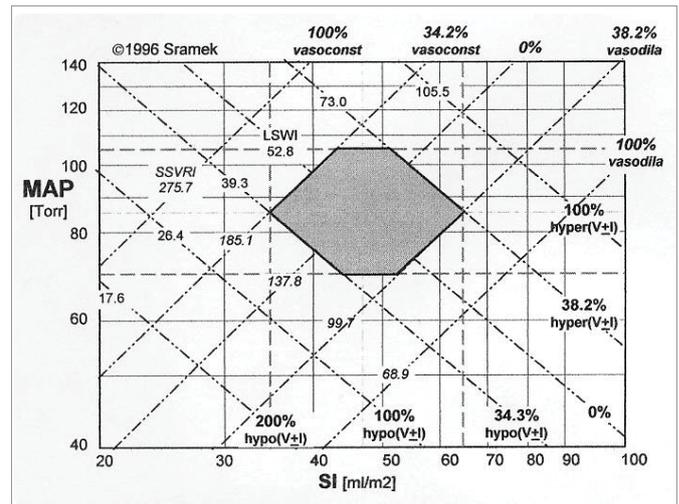
Figure 1: HOTMAN - System® thoracic impedance monitors display. The discontinuous diagonals represent the volemic and vasotonal states, respectively. Shaded rhomb in the center corresponds to the optimum hemodynamic state; MAP: Mean Arterial Pressure; SI: Stroke Index.
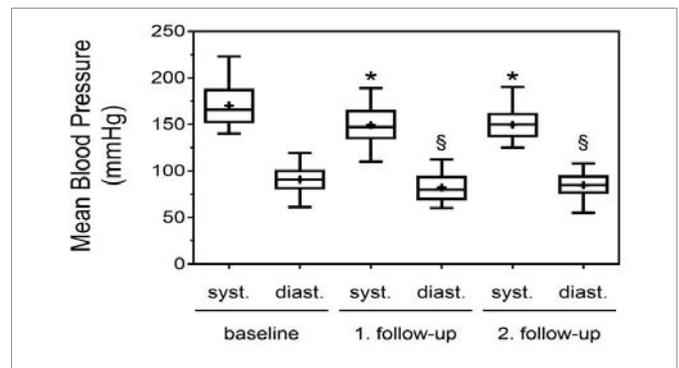
Figure 2: Thorax impedance guided TRH management; results of office blood pressure measurements at baseline, six and twelve months follow-up. Significant reductions of systolic and diastolic blood pressures on follow-up are shown between the sixth and twelfth months follow-up no further significant blood pressure reduction was noted; +mean and median are presented; *significance vs. baseline systolic; §significant vs. baseline diastolic, p ≤ 0.05
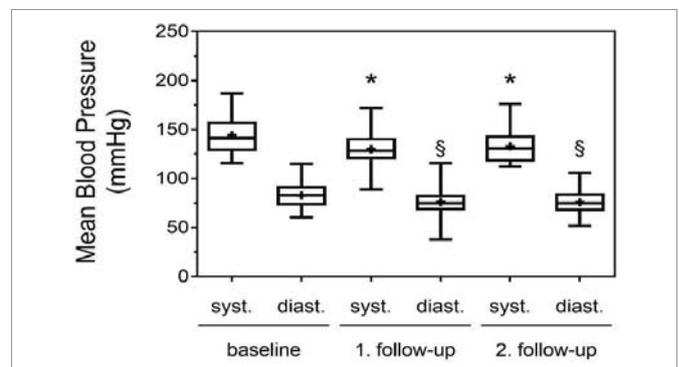
Figure 3: Thorax impedance guided TRH management; results of ambulatory blood pressure measurements at baseline, six and twelve months follow-up. Significant reductions of systolic and diastolic blood pressures on follow-up are shown between the sixth and twelfth months follow-up no further significant blood pressure reduction was noted; +mean and median are presented; *significance vs. baseline systolic; §significant vs. baseline diastolic, p ≤ 0.05.

blood pressure measurements at six months no additional statistically significant reduction in blood pressure measurements at twelve months was observed (Figure 5).

Overall, after 12 months follow-up 20 patients (40%) have become normotensive, in 17 patients (35%) the blood pressure control improved without reaching normotensive blood pressure range, in 10 patients (20%) no improvement in blood pressure control was achieved and in 3 patients (6%) blood pressure deteriorated.

Measurements of the hemodynamic modulators demonstrated the highest prevalence and the highest deviation in the volume status; at baseline 47 out of 50 (94%) patients were hypervolemic with a mean hypervolemia of $136 \pm 134\%$; one patient was hypovolemic and two patients were normovolemic. At six months follow-up 49 patients were hypervolemic and 1 patient was normovolemic; however, the degree of hypervolemia was compared to baseline significantly reduced ($73.7 \pm 26.4\%$; $p = 0.002$). At twelve months follow-up no further changes in volume status were observed.

DISCUSSION

Compared to hypertension TRH is associated with higher organ-related morbidity and worse clinical prognosis [6]. Currently, patients with TRH are largely treated employing the empiricism- based algorithms [7]. Using this approach variable, yet significant number of patients features suboptimal blood pressure control [1,8,9].

We hypothesized, that in patients with TRH medication prescriptions based on the non-invasive measurements of the

hemodynamic variables using the thorax impedance might improve blood pressure control.

By targeting the blood pressure modulator with the highest deviation from the normal value significant reduction in both systolic and diastolic blood pressure as determined by office and ambulatory blood pressure measurements were achieved by six months with no further significant changes at twelve months follow-up. Furthermore, the 24-hours average systolic and diastolic blood pressures during the daytime and in the night have followed the same pattern. In addition, 40% of patients became normotensive; in 34% of patients blood pressure control improved. Compared with the published results of the standard guideline- directed therapy in patients with TRH [10] slightly improved response rate and blood pressure control using the hemodynamic guidance has been achieved. Although significant improvement in blood pressure levels were achieved after six months of treatment were achieved no further therapy effect was achieved at twelve months follow-up. While the reasons for blood pressure resistance to therapy between six and twelve months remain obscure, slacking compliance, secondary compensatory responses to antihypertensives, obesity- associated resistance to antihypertensives and other factors might have been involved [11-15].

LIMITATIONS

The study was designed to proof the concept; not as blinded randomized trial. The number of patients included in the study has been limited to fifty and a study with a larger number of patients may be needed to confirm the results. The study reflects the real-life constrains typically encountered in an out-patient referral office where only limited control of patients' medication at baseline and the follow-up points was possible. Changes in prescribed medication due to hospital treatments or referring physicians' preferences might have partially affected the outcome of the study. The study could have benefitted from quantitative echocardiography of the left ventricular function and morphology, rather than being employed only at baseline to exclude secondary cardiac causes of hypertension. Finally, the initially administered renin antagonist aliskiren had to be discontinued on follow-up due to withdrawal of the drug from the market might have also impacted on the outcome.

SUMMARY

The study has proven that the concept of hemodynamically-guided management of patients with TRH is feasible and promising.
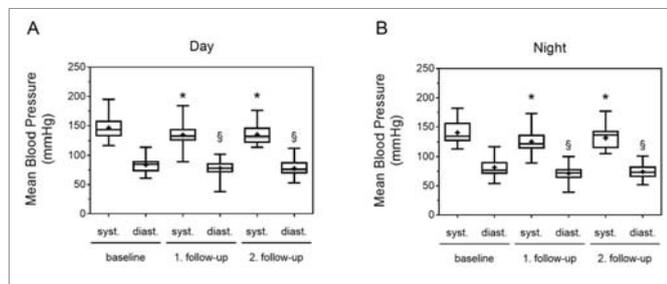
Figure 4: Thorax impedance guided TRH management; results of ambulatory blood pressure measurements at baseline, six and twelve months follow-up; A) day and B) night measurements. Significant reduction in mean blood pressure was measured at 6 months follow-up and there were no further significant changes in blood pressure at 12 months follow-up.
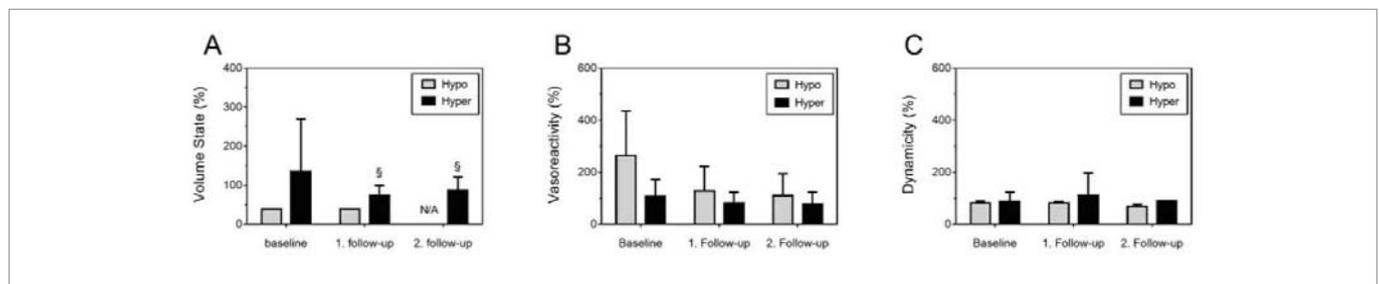
Figure 5: Volemic, vasotonal and dynamicity states at baseline, six and twelve months follow-up. In the studied cohort volemic states were closely related to the measured blood pressures,
A: In contrast, vaso reactivity
B: Dynamicity
C: As determined by the thorax impedance were not significantly correlated with blood pressure measurements.

Table 3: Summary of cardiovascular risk factor in the entire cohort, in males and in females.

Age (years)	60,82 ± 10,34 N = 50	62,95 ± 11,95 N = 28	62,95 ± 11,95 N = 22
BMI	31,25 ± 5,70 N = 50	33,86 ± 5,47 N = 28	32,40 ± 5,75 N = 22
Diabetes Mellitus	N = 19	N = 9	N = 10
Dyslipidemia	N = 21	N = 10	N = 11
Chronic Renal Insufficiency	N = 9	N = 3	N = 6

However, to confirm the clinical utility of the thorax impedance-based non-invasive management of patients with TRH larger blinded and randomized trial will be necessary.

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