Multidisciplinary Lifestyle Interventions In The Management of Resistant Hypertension

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Abstract

Resistant hypertension renders patients refractory to pharmacological treatment and is closely associated with excess weight and high cardiovascular risk. Resistant hypertension and obesity-associated hypertension share highly interrelated and interacting pathogenic mechanisms exacerbated by adiposity that propagate end organ damage including chronic kidney disease and cardiovascular disease. Perhaps it is time to contemplate in the overall management of hypertension, invasive procedures focused on weight loss. Lifestyle interventions improved results from pharmacotherapy alone in a cohort of patients with resistant hypertension. After 6 months of intensive multidisciplinary care, we found significant reductions in blood pressure, body mass index, and antihypertensive medication burden with improvement in cardiovascular disease biomarkers. Increased physical activity and weight loss appeared to be significant factors. Weight-loss drugs are generally ineffective but the impact of laparoscopic sleeve gastrectomy in another cohort of patients with obesity grade 3 and hypertension, was relevant with hypertension remission in more than 50% of cases and significant reductions in blood pressure and medication burden in those who remained hypertensive. Our results suggest the need to define in future studies and selected patients the potential role of combining medical multidisciplinary care with surgical interventions in the management of patients with resistant hypertension and high cardiovascular risk.

Introduction

The prevalence of hypertension and the associated risk of death are rising throughout the world despite the availability of low-cost drugs with proven efficiency ¹. Failures in treatment, however, are relatively frequent due to lack of adherence or misdiagnosis. The problem is especially important in patients with essential resistant hypertension (RHT) who do not respond well even to the combination of multiple drugs. Patients with RHT represent $\geq 10\%$ of the antihypertensive drug-treated population, and obesity contributes to deficient control that propagates the greater mortality and morbidity observed in this population ²⁻⁴. The diagnosis requires management of suboptimal adherence and secondary causes of hypertension with ambulatory blood pressure (BP) above goal despite the concurrent use of at least 3 medications of different classes, including a diuretic, at maximal dosage ^{5,6}. Consequently, treatment is complex and faces significant challenges associated with specific skills in lifestyle manipulation, cardiovascular diseases, renal dysfunction, and drug therapy ^{7,8}. There are guidelines for pharmacological treatment and several drug combinations have been assessed but multi-drug treatment alone is not as effective as it would be desirable with failures in BP control and frequent adverse effects that cause considerable concern ^{2,8,9}. Failures in management have prompted the relatively recent assay of invasive procedures, with controversial effectiveness, which include renal nerve ablation, baroreceptor stimulation, and novel experimental devices ¹⁰⁻¹². Surprisingly, the impact of lifestyle interventions has not been fully established in RHT ¹³⁻¹⁶. Multiple factors are involved but a high prevalence of obesity, as well as unpredictable hemodynamic effects of many medications, complicates not only the treatment of hypertension but also the associated cardiovascular risk ¹⁷. Conversely, hypertension per se contributes

to the increased risk of obesity, suggesting that joint therapeutic targeting might be instrumental for successful control ¹⁸. Increased morbidity and the lack of long-term studies with cardiovascular outcomes have hampered the understanding of the impact of surgically induced weight loss, which provides more permanent weight reduction than lifestyle medication, on the management of hypertension. Broadly, obesity-associated factors that alter hemodynamics throughout the body and control systemic BP are likely underlying pathomechanisms that need to be clarified in RHT ¹⁹.

In this study, we demonstrate the benefits of intensive, multidisciplinary care in patients with long-established RHT and high cardiovascular risk in which increased physical activity and weight loss appeared to be relevant determinants. To further confirm the complicating role of obesity in managing hypertension ²⁰, we explored in a separate cohort of hypertensive patients with severe obesity the impact of weight loss surgery ^{21,22}. A relatively safe procedure was associated with dramatic declines in BP, withdrawal of medications, and hypertension remission. Possibly, the combination of medical lifestyle interventions and surgical weight management might attenuate long-term cardiovascular risk in patients with RHT.

Results

Patients with true essential resistant hypertension were recruited with strict diagnostic criteria and followed a multidisciplinary lifestyle intervention for 6 months as described below. The high attrition rate indicated that our proposal was demanding for ambulatory patients and data are reported for the 30 patients who successfully fulfilled all programmed visits (Supplementary Fig. S1). Patients were ethnically homogeneous and sedentary at baseline with excess weight and a significant proportion of patients with obesity (mean body mass index (BMI), 33.1 ± 4.4 Kg/m²). There were more men than women, and on average the time since the first diagnosis of hypertension was 16 years. Clinical examination indicated that patients, on average, were at high cardiovascular risk (Table 1) and clinical records highlighted previous clinical cardiovascular disease in 7 patients (coronary heart disease, n = 2; cerebrovascular disease, n = 3; heart failure, n = 1; atrial fibrillation, n = 1). Laboratory assessment revealed that the urinary albumin-to-creatinine ratio was responsive to treatment, especially in patients (n = 5) with an estimated glomerular filtration rate slightly below 60 ml/min (Supplementary Table S1). A significant proportion of patients (n = 20 (71%)) had at least one marker for cerebral small vessel disease but the cognitive level, according to MoCA score adjusted for age and education level, did not vary during the intervention.

Table 1
Characteristics of patients included in the study.

	Patients with RHT (n=30)
Age (years)	59.6 ± 8.8
Sex, men, n (%)	22 (66)
BMI (kg/m ²)	33.1 ± 4.4
Waist circumference (m)	1.1 ± 0.1
Time since RHT diagnosis (years)	15.9 (9.4)
24 hours SBP (mmHg)	138.3 ± 20.1
24 hours DBP (mmHg)	85.7 ± 12.1
T2DM, n (%)	12 (36)
Dyslipidemia, n (%)	23 (76)
OSAS, n (%)	18 (60)
Metabolic syndrome, n (%)	19 (63)
Atrial fibrillation, n (%)	1 (3)
Right branch bundle block, n (%)	4 (13)
Left branch bundle block, n (%)	2 (6)
Left ventricular hypertrophy, n (%)	27 (90)
Heart rate (beats/min)	72.2 ± 10.4
PWV > 10 m/seg, n (%)	7 (23)
Ankle-brachial index < 0.9, n (%)	1 (3)
Left atrial enlargement, n (%)	25 (83)
Carotid artery plaque, n (%)	23 (76)
BMI: body mass index; DBP: diastolic blood pressure; OSAS: obstructive sleep apnea syndrome; PWV: pulse wave velocity; RHT: resistant hypertension; SBP: systolic blood pressure; T2DM: type 2 diabetes mellitus.	

From baseline to the end of the study, mean changes in ambulatory BP were significantly improved and most patients achieved the desired goal, with significantly lower morning BP surge. Changes in circadian pattern distribution and BP variability did not achieve statistical significance ($p=0.061$) but there were more non-dippers and fewer dippers (Fig. 1, Table 2). The decrease in BP was not homogeneous (Fig. 2) and some patients were non-responders ($n=7$). We did not find objective reasons for this lack of response

but multivariate analysis and random forest identified as best predictors the concentration of renin and C-reactive protein in plasma, and the protein and albumin excretion in urine (Supplementary Fig. S2). Of note, these were the only laboratory variables with significant changes after the intervention likely indicating heterogeneous improvement in the inflammatory status and/or changes in prescribed drugs (Supplementary Table S1). BP reduction was also accompanied by a significant decrease in the average daily medication both in number and daily-defined dose (Fig. 3A, B). Changes in BP and all measured variables during the intervention positively affected the cardiovascular risk (Supplementary Fig. S3) and there was a significant decrease in heart rate and arterial stiffness, as well as improvement in calculated cardiovascular risk scores, at the end of the study (Fig. 3C-E). We also found a potential improvement in endothelial dysfunction but the variations in arterial diameter using reactive hyperemia ($2.7 \pm 3.6\%$ at baseline and $5.4 \pm 6.9\%$ after intervention) did not reach statistical significance.

Table 2
Blood pressure parameters registered by the monitoring arterial blood pressure system.

	Baseline	After intervention	p-value
Peripheral blood pressure			
24 hour SBP (mmHg)	138.3 ± 20.1	124.3 ± 11.8	1.6x10⁻⁵
24 hour DBP (mmHg)	85.7 ± 12.1	77.2 ± 10.4	2x10⁻⁵
Daytime SBP (mmHg)	141.2 ± 18.8	126.1 ± 11	2.5x10⁻⁶
Daytime DBP (mmHg)	88.6 ± 11.6	79.7 ± 10.4	7.3x10⁻⁶
Nighttime SBP (mmHg)	131 ± 25.3	121.1 ± 17.7	0.013
Nighttime DBP (mmHg)	77.9 ± 15.3	72 ± 11.9	0.014
Heart rate (beats/min)	72.2 ± 10.4	69.3 ± 10.9	0.038
Central hemodynamics			
Central SBP 24 hour (mmHg)	126.9 ± 17.7	114.1 ± 10.6	6.7x10⁻⁶
Central DBP 24 hour (mmHg)	85.5 ± 12.3	79.5 ± 10.4	1.8x10⁻⁵
Central daytime SBP (mmHg)	128.4 ± 16.5	115.4 ± 10.8	2.5x10⁻⁶
Central nighttime DBP (mmHg)	90.2 ± 12.1	81.4 ± 10.3	1.3x10⁻⁶
Central daytime SBP (mmHg)	122.3 ± 25.8	110.9 ± 14.3	0.007
Central nighttime DBP (mmHg)	80.1 ± 15.7	73.4 ± 12.1	0.013
Cardiac output (L/min)	6.3 ± 7	6.3 ± 8.6	0.013
Peripheral vascular resistance (mmHg/L)	1.3 ± 0.2	1.4 ± 0.8	0.079
Variability of arterial pressure			
Systolic mean (mmHg)	132.5 ± 16	126.3 ± 14.1	0.064
Diastolic mean (mmHg)	82.5 ± 11.2	78.5 ± 10.9	0.049
Systolic SD (mmHg)	16.8 ± 4.9	15.1 ± 3.9	0.184
Diastolic SD (mmHg)	12.6 ± 3.1	11.7 ± 2.6	0.178
Systolic CV (mmHg)	12.6 ± 3.2	11.9 ± 2.5	0.229
Diastolic CV (mmHg)	15.4 ± 3.9	15.1 ± 3.3	0.685
SBP: systolic blood pressure; DBP: diastolic blood pressure; MBPS: morning blood pressure surge; SD: standard deviation; CV: variation coefficient; ARV: average real variability.			

	Baseline	After intervention	p-value
Systolic ARV (mmHg)	14.5 ± 5.3	13.6 ± 5	0.375
Diastolic ARV (mmHg)	11.3 ± 3.6	10.3 ± 3.4	0.243
Weighted SD (mmHg)	22.3 ± 2	22.4 ± 1.5	0.948
Surge morning			
Sleep-through MBPS (mmHg)	26 ± 14.5	18.4 ± 14.9	0.061
Pre-waking MBPS (mmHg)	23.2 ± 20.5	12.4 ± 11.5	0.036
SBP: systolic blood pressure; DBP: diastolic blood pressure; MBPS: morning blood pressure surge; SD: standard deviation; CV: variation coefficient; ARV: average real variability.			

At baseline, patients were sedentary and considered “unfit” or “low fit” with poor dietary habits. The relationship of lifestyle interventions with weight loss and increased physical activity was relevant. As a group, weight loss was significant but this was not appreciated in measurements of waist circumference (Fig. 4A, B). BMI correlated with nighttime BP and 24-hour DBP, both central and peripheral, at baseline but this association was no longer significant at the end of the study (Fig. 4C, D). Self-reported satisfaction with dietary advice was excellent although adherence to a salt-free diet was deemed suboptimal in some patients with good response. All patients moved to a higher fitness category after the intervention. Stimulation techniques and provision of pedometers were successful and patients walked routinely more than 60 min daily (measured as average steps per week) and were engaged in resistance training for two non-consecutive days per week. It is, therefore, likely that efforts focused on weight loss and increased physical activity may be beneficial in patients with RHT and high cardiovascular risk.

Weight-loss drugs are generally ineffective in the long-term and weight loss surgery provides more permanent weight reduction and improved fitness but it is certainly an invasive procedure. Recent advances, however, suggest that more simple and safe techniques, exemplified by laparoscopic sleeve gastrectomy (LSG), provide excellent results in obesity-related comorbidities²². However, only a few patients with RHT fulfilled current requirements in our area (i.e., BMI > 35 kg/m²). We then explored the impact of LSG in another cohort of patients with obesity grade 3 and steady hypertension (n = 48), which was difficult to control even with ≥2 medications at maximum doses. Of note and despite the common association between obesity and hypertension, none of these patients had diagnostic criteria for RHT. Patients in this cohort were ethnically homogeneous and on average middle-aged adults, mostly female. Selected characteristics at baseline and after surgery are reported in Supplementary Table S2. The surgically induced metabolic improvement was significant and the BMI decreased from 56 ± 6.9 to 33.1 ± 4.9 Kg/m² at the end of the 12-month period of observation. Reductions in BP levels were significant and more evident in systolic BP. Moreover, hypertension was reversed in 28 patients and those that remained hypertensive were taking less antihypertensive treatment measured as daily medication per patient and dosage (Fig. 5). We did not find clear reasons to explain that hypertension remission was limited to some

patients. However, those that still required medication had more severe metabolic complications at baseline. Although age and reduction in BMI were similar in patients with and without hypertension after surgery, systolic BP was closely associated with age (Supplementary Fig. S4). Our data suggest highly interrelated mechanisms in the development of hypertension in obesity. Conceivably, clinically meaningful reductions in BP achieved with lifestyle interventions can be complemented by surgical procedures in patients with RHT and high cardiovascular risk.

Discussion

It is important to identify effective procedures for lowering BP in patients that do not respond to multiple antihypertensive medications. The prognosis of patients with RHT is ominous and associated with higher mortality, higher prevalence of end-organ damage and higher cardiovascular risk than in controlled hypertensive patients²³. A few studies currently recommend invasive procedures, most notably renal denervation, with controversial results²⁴ but it is important to consider that an increasing number of cases occur in people with weight excess. Recent results from a randomized clinical trial demonstrated that diet and exercise training delivered in a cardiac rehabilitation setting could lower BP in patients with RHT, although the effectiveness of lifestyle modifications is yet to be established^{9,25,26}. We have obtained similar BP reductions with a 6-month organizational change within a personalized care based on multiple ambulatory visits and intensive intervention. However, this prospective program was challenging for both patients and physicians and required the coordination of a multidisciplinary team. We acknowledge that cost-effectiveness and generalizability of our findings need to be re-evaluated because long-term effectiveness remains uncertain. Another limitation is that BP in some patients was above goal at baseline. It is difficult to compare data among trials but BP reductions were numerically larger than those observed in other interventions^{26–29}. There was a large mean reduction in 24 h ambulatory BP (-14.0/-8.5 mmHg (SBP/DBP)) with a significant reduction in pill burden and prescribed dosage. For comparison, ultrasound-based renal denervation is associated with reductions in ambulatory SBP of -9.4 mmHg³⁰. Our intervention also improved several cardiovascular biomarkers. The improvement in nighttime pressures may denote the importance of controlling the time of uninterrupted sleep, which has been important to reduce mortality risk³¹. Similarly, BP reductions of this magnitude combined with a significant reduction in heart rate and beneficial variations in arterial stiffness have been associated with improved cardiovascular outcomes in patients with hypertension^{32,33}. The significant reduction in morning BP surge and improved fitness^{34,35}, and the significant differences in albumin excretion and C-reactive protein may also translate to improved cardiovascular risk³⁶.

Therefore, high quality interventions, likely associated with weight loss and fitness, yield positive outcomes in hypertension. The epidemic burden of obesity partially explains the growing problem that RHT represents in the hypertension field and shared pathophysiologic mechanisms are exacerbated by greater degrees of adiposity^{37,38}. We have not found a clear association between weight loss and BP reductions and there are a number of reasons to expect that long-term benefits of healthful behaviors are unlikely without persisting support and long-term adherence³⁹. In an effort to demonstrate whether

potential benefits in the management of RHT result in a reduction of major cardiovascular events, invasive procedures are open to debate. In this scenario, we contemplate LSG as a conceivable candidate. Perhaps it was ethically challenging in the past but our observations suggest that not all patients but some selected cases may be qualified for current laparoscopic procedures. Morbidity is relatively low and modern techniques promote long-term major weight loss associated with the metabolic and inflammatory improvement of other obesity-associated comorbidities^{21,22,40}. In this study we found hypertension remission in a significant number of cases and LSG was effective for reducing number and dosage of antihypertensive drugs. Our findings support those from a previous report using Roux-en-Y gastric bypass in hypertensive patients with grade 1 and 2 obesity⁴¹. Data are not interchangeable and of difficult interpretation because the unknown but multifactorial nature of resistant hypertension prevents speculation on the actual importance of weight loss. However, surgically induced weight loss might decrease the burden of RHT associated with obesity⁴².

In conclusion, our data may aid healthcare decision-making in patients with RHT at high risk and poor prognosis. Multidisciplinary care maximizing lifestyle intervention is a beneficial therapeutic strategy even in patients with poor fitness and major cardiovascular damage. Presumably, earlier aggressive management could be preventive and the addition of LSG to the treatment of obese patients with RHT can be promising.

Methods

Participants

This is a coordinated study in two settings to examine both medically and surgically aggressive approaches to treat hypertension. Each Institutional Review Ethics Committee approved all procedures and design of the study, all subjects gave their informed consent, and all methods were performed in accordance with the current guidelines and regulations. One cohort was used to test the impact of intensive and multidisciplinary management on true essential RHT. The lead clinician initially included 50 patients from those referred to the Hypertension Clinic of the Vall d'Hebron hospital in Barcelona but final analysis was based on 30 patients. Six participants withdrew consent before completing the full program, and fourteen missed several of their follow-up visits indicating irreconcilabilities with their normal life (Supplementary Fig. S1, Table 1). The other cohort was used to test the effect of surgically induced weight loss on BP. Among patients with grade 3 obesity that underwent LSG at the Hospital Sant Joan, in Reus, all hypertensive patients treated with ≥ 2 antihypertensive drugs at maximum doses ($n = 48$) were included.

Clinical And Laboratory Assessment

Recruited patients with true essential RHT were reevaluated at baseline to ensure the diagnosis. Polysomnography assessed obstructive sleep apnea and results were used to maximize the time of

uninterrupted sleep with continuous positive airway pressure therapy ⁴³. Time of uninterrupted sleep (≥ 6 hours) was recorded monthly. The lead clinician constantly reviewed medications and supervised adherence according to guidelines ². Patients initiated periodic visits (at least monthly) during 6-months with a dietician to adapt individualized healthy and salt-free diet ⁴⁴, with a specialist in controlled exercise program ⁴⁵, and with a psychologist to identify and treat relevant psychosocial factors, to assess potential cognitive decline, and to monitor adherence ⁴⁶. Laboratory measurements were performed following standard procedures to explore metabolic risks and several explorations were indicated to obtain paired data at baseline and after the follow-up. Brain magnetic resonance imaging was used to explore cerebrovascular disease ⁴⁷. Echocardiography was used to explore cardiac geometry and left ventricular function ⁴⁸. Arterial stiffness and carotid intima-media thickness was explored using a high frequency echography with a linear transducer, as described ⁴⁹. Carotid-femoral pulse wave velocity measurements and central augmentation index calculated from the pulse wave analysis were used as surrogates of arterial stiffness ⁵⁰. Endothelial function was assessed using the brachial artery flow-mediated vasodilation ⁵¹. 24 h ambulatory BP measurements, with at least 80% valid readings, were performed on weekdays with the Mobil-o-Graft automatic device following the European Society of hypertension guidelines ⁵². Circadian patterns, BP variability and morning BP surge were defined as described ^{53,54}. Patients with extreme obesity were explored within the EPIMET study, immediately before surgery and 12 months after surgery, and details on LSG and clinical procedures have been previously described ⁵⁵.

Statistics

Qualitative variables were described as number and percentage and quantitative variables were described as mean and standard deviation. Paired t-test, chi-square test and McNemar test were performed on SPSS 24 (IBM, Chicago, IL, USA). Bar plots, box plots and pie charts were drawn with GraphPad Prism 6.01 (GraphPad Software, San Diego, CA, USA). P values were considered significant when <0.05 . R (version 4.0.2) was employed to calculate the Pearson pairwise correlation matrices through the Performance/ Analytics package (<https://github.com/braverock/PerformanceAnalytics>) with the function "chart.correlation". MetaboAnalystR ⁵⁶ was used to run Partial Least Square - Discriminant Analysis (PLS-DA) to obtain the three-dimensional synchronized plot and variables importance in projection scores in order to assess predictive values. From MetaboAnalystR, we also obtained the hierarchical clustered heatmap ranked by t-test to show the top 15 variables with the most discriminant capacity, and the hierarchically clustered correlation heatmaps. Scikit-learn package ⁵⁷ in Python (version 3.8.12) was used to implement multiple linear regression and random forest model. The variable response of patients to treatment was determined by calculating the ratio of all measures of BP taken at baseline and after follow-up. Results were shown in bar plots using log2 scale.

Declarations

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Authors' contributions

Concept and design: EE, JJ, DS; Data collection: All authors; Data analysis: EE, HC, JJ, DS; Drafting of the manuscript: EE, JJ, HC; Statistical support: Dedicated staff from both Hospitals; Critical revision of the manuscript: All authors.

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Additional information

The authors have no competing interests to declare.

Data availability

The datasets generated during the current study have been deposited at repositories from the Hospital de la Vall d'Hebron and the Universitat Rovira i Virgili, which will be accessible upon publication of the manuscript. The lead clinician (EE) will attend all reasonable requests.

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Figures

Figure 1

Multidisciplinary lifestyle interventions reduce blood pressure in patients with resistant hypertension. Individual changes in systolic (SBP) and diastolic (DBP) blood pressure from baseline to the end of the intervention.

Figure 2

The response to interventions was not homogeneous. (a) The fold change in mean blood pressure distinguished a group of non-responders. Changes in individual SBP (b) and DBP (c) measurements in patients arbitrarily distributed according to the degree of response.

Figure 3

Clinical outcomes associated with hypertension improved after medical treatment. (a) Mean number of medications per patient. (b) Detailed use of antihypertensive classes. (c) Variation in cardiovascular risk scores. (d) Heart rate and (e) Surrogates for arterial stiffness.

Figure 4

The relationship between weight loss and blood pressure in patients with resistant hypertension were modified after interventions. (a) Body mass index (BMI). (b) Waist circumference. Significant correlation plots with fitted line at baseline (c) of systolic (SBP) and diastolic (DBP) blood pressure with BMI, were not maintained after intervention (d). Pearson's correlation coefficient is represented in the upper and right part of each plot, and significance with and asterisk (*) and numbers in bold.

Figure 5

Surgically induced weight loss decreased the burden of steady hypertension in patients with extreme obesity. (a) Body mass index (BMI). (b, c) Systolic and diastolic blood pressure levels decreased after surgery. (d) Patients with hypertension after surgery. (e) Daily medications per patient. (f) Prescription of antihypertensive drugs after surgery.

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