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CLINICAL TRIAL

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Effect of baroreflex activation therapy on dipping pattern in patients with resistant hypertension

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Observational study (Headline and registration): Observational studies do not meet the FDA, NIH, or ICMJE definitions of clinical trials, and are not required to be registered.

Abstract

A relevant number of patients with resistant hypertension do not achieve blood pressure (BP) dipping during nighttime. This inadequate nocturnal BP reduction is associated with elevated cardiovascular risks. The aim of this study was to evaluate whether a nighttime intensification of BAT might improve nocturnal BP dipping. In this prospective observational study, non-dippers treated with BAT for at least 6 months were included. BAT programming was modified in a two-step intensification of nighttime stimulation at baseline and week 6. Twenty-four hours ambulatory BP (ABP) was measured at inclusion and after 3 months. A number of 24 patients with non- or inverted dipping pattern, treated with BAT for a median of 44 months (IQR 25–52) were included. At baseline of the study, patients were 66 ± 9 years old, had a BMI of 33 ± 6 kg/m^2, showed an office BP of 135 ± 22/72 ± 10 mmHg, and took a median number of antihypertensives of 6 (IQR 4–9). Nighttime stimulation of BAT was adapted by an intensification of pulse width from 237 ± 161 to 267 ± 170 μs ($p = .003$) while frequency ($p = .10$) and amplitude ($p = .95$) remained unchanged. Uptitration of BAT programming resulted in an increase of systolic dipping from 2 ± 6 to 6 ± 8% ($p = .03$) accompanied with a significant improvement of dipping pattern ($p = .02$). Twenty four hours ABP, day- and nighttime ABP remained unchanged. Programming of an intensified nighttime BAT interval improved dipping profile in patients treated with BAT, while the overall 24 h ABP did not change. Whether the improved dipping response contributes to a reduction of cardiovascular risk beyond the BP-lowering effects of BAT, however, remains to be shown.

KEYWORDS
ambulatory blood pressure monitoring, baroreflex activation therapy, nocturnal dipping, resistant hypertension

Manuel Wallbach and Ellen Born are countributed equally.

1 | INTRODUCTION

Baroreflex Activation Therapy (BAT) represents an interventional treatment option in patients with resistant hypertension (HTN)[1,2] and congestive heart failure with reduced ejection fraction[3,4] by modulation of the autonomic nervous system leading to an inhibition of the sympathetic nervous system and an increase of parasympathetic activity.[5] For BAT, an implantable, programmable pulse generator is placed underneath the pectoralis major muscle.[6,7] The device mimics the body's blood pressure (BP) regulation by electrically activating the baroreceptors that sense an aberrant increase of the BP level.[8] Consequently, central sympathetic outflow is reduced in a sustained manner leading to BP reduction and potential organ protective effects.[9–14] BAT offers the possibility of individual programming by modification of pulse width, frequency, and amplitude. This technical capability allows to adjust the therapy very precisely to patient's needs. One example of its technical capabilities is the programming of different stimulation periods throughout the day. The physiologically BP fluctuates with a pattern that follows a circadian rhythm with a peaking in the early morning and a dipping during nighttime.[15] Circadian rhythm is generated in the anterior hypothalamus and the autonomic nervous system, which is suggested to play a role in its translation to BP changes.[16]

Adequate nocturnal dipping is defined as a decrease in nocturnal BP of 10% or more relative to daytime BP. It is suggested that non-dipping is associated with an increase in sympathetic nervous activity during nighttime.[17,18] Moreover, many resistant hypertensives do not show nighttime dipping, which is associated with an increased cardiovascular risk and end-organ damage.[19] Renal denervation is another interventional BP-lowering approach targeting sympathetic nervous system. For renal denervation, there are both experimental and clinical references, indicating an effect to improve dipping patterns.[20,21] BAT with its possibility to program a separate night interval might be effective in improving nighttime dipping. However, data on the effects of BAT on dipping pattern are lacking so far. Thus, the objective of this study was to examine whether programming of an intensified nighttime stimulation interval improves the dipping profile in long-term BAT treated patients.

2 | METHODS

2.1 | Participants

For this observation study patients with resistant HTN, who were treated with BAT for at least 6 months and exhibited a stable antihypertensive drug regime for at least 6 weeks were screened with ambulatory BP monitoring (ABP). All patients suffered from resistant HTN before BAT implantation according to the ESH Guidelines 2013.[22] Initially, evaluation and indication for the use of BAT was performed according to ESH guidelines 2013.[22] However, following our own experiences and evaluations, we adapted our approach early on, which is in line with the consensus recommendations published in 2017.[23] Patients with non- or inverted dipping were enrolled. Patients with sleep apnea syndrome, shift working or circumstances that make it difficult or impossible to interpret the results (e.g., sleep disorders etc.) were excluded from this study.

All patients provided informed consent before the initiation of protocol-mandated procedures. The study was approved by the local Ethical Committee of Göttingen (19/9/2011). The investigation conforms to the principles outlined in the Declaration of Helsinki.

2.2 | Office and ambulatory BP monitoring

Office BP was measured on each arm. The arm with the higher BP was used for all subsequent readings. Brachial BP of the arm was recorded after 10 min of supine rest using a semiautomatic oscillometric device (Bosch + Sohn GmbH, Jungingen, Germany) two times within a 3 min interval according to the Joint National Committee Guidelines.[24] The mean values of these two measurements were averaged. BP was measured on the same side throughout the study.

ABP was performed using an oscillometric Spacelabs Model 90207 Recorder (Spacelabs Healthcare, Nürnberg, Germany) with readings taken every 15 min during daytime and every 30 min during nighttime. Ambulatory blood pressure (ABP) readings were averaged for 24 h, day (6 am to 10 pm), and night (10 pm to 6 am). Patients were assessed while adhering to their usual diurnal activity and nighttime sleep routine. According to the ESC/ESH guidelines, only recordings with >70% valid measurements, at least 20 valid awake (≥2 valid day-time/h), and 7 valid asleep (≥ 1 valid night-time/h) BP measurements were included in the analysis.[22] Patients were graded according to their dipping pattern into three groups: dippers (nighttime BP falls ≥10% and ≤20%), non-dippers (nighttime BP falls <10% and ≥0%), and inverted dippers (nighttime BP > daytime BP).

2.3 | BAT programming

For BAT, the Barostim neo (CVRx, Minneapolis, USA) was used, as described previously.[13,14,25] For identified non-dippers, BAT programming was modified as part of the clinical routine in a two-stepped intensification of nighttime stimulation at study baseline and after 6 weeks, while daytime BAT mode remained unchanged.

Based on previous experience from our center as well as prior literature, there was no evidence for an optimized standard programming. In fact, patients treated with BAT in the routine showed highly variable response and tolerability in respect to different BAT stimulation settings, resulting in an individual titration of BAT programming within the present study. For this purpose, the parameters pulse amplitude (1–20 mA), pulse width (15–500 μs) and frequency (10–100 HZ) were programmed individually. Programming with the largest effect on BP in absence of acute side effects was applied as a nighttime pacing interval from 22:00 to 06:00.

2.4 | Adaption of antihypertensives, adverse events, and response

Antihypertensive medication was reduced if one or more of the following parameters were fulfilled: a) BP was below the individual target, b) patients with BP above target developing severe symptoms associated with BP reduction (e.g., dizziness), c) typical with antihypertensive medication associated side effects arose (e.g., hyperkalemia using aldosterone antagonist). An adaptation of the medication by the family doctor was not excluded. All patients underwent a complete history and physical examination, assessment of vital signs, and review of medications. Relevant concomitant diseases were evaluated by anamnesis and chart reviews. Patients were interviewed whether they had taken their complete medication at their defined dose. Adverse events were evaluated and graded as described before.[26] Patients were considered as responder, if they experienced an improvement in systolic dipping pattern after the 3 months observation period.

2.5 | Statistical analysis

The data were evaluated using the statistical Software GraphPad Prism 8 and Microsoft Excel (Version 16.60). To analyze longitudinal differences, a paired 2-sided T-Test was used. Results are expressed as mean ± standard deviation (SD) or median and interquartile range (IQR) or number with percentage for categorical variables. Multiple characteristics of responders and non-responders were compared either by using an independent T-Test or the Chi-square test, where appropriate. Two-way ANOVA was performed to analyze the effect of BAT in these two subgroups. The threshold for statistical significance was chosen to be $p < .05$.

3 | RESULTS

3.1 | Baseline characteristics

A number of 45 patients who underwent prior BAT implantation in our hypertension center and are regularly monitored in our outpatient clinic were screened for the present study. Adequate dipping was observed in 12 patients, 5 patients were already deceased, and 4 patients refused study participation. Consecutively, a number of 24 patients could be included into the present study. At baseline mean age of 66 ± 9 years, mean body mass index (BMI) was 32 ± 6 kg/m^2, 12 patients (50%) suffered from diabetes mellitus, 16 patients (67%) from hyperlipoproteinemia, 2 patients (8%) were current, and 10 (42%) former smokers. Relevant end-organ damages included former apoplexy in 5 patients (21%) and myocardial infarction in 3 (13%), congestive heart failure in 6 (25%), and chronic kidney disease stadium ≥3 in 12 patients (50%). Indeed, patients included in the present study seems to be at high risk, as the vast majority of patients (96%) had signs of end-organ damage, indicating BAT was used for secondary BP treatment in this cohort. On average, patients were treated for HTN with BAT for a median of 44 months (IQR 25–52) in addition to a median number of antihypertensive drugs of 6.0 (IQR 4–9) antihypertensive drugs at baseline. Five patients (21%) underwent renal denervation prior to the BAT treatment. Baseline characteristics are summarized in Table 1. One patient was a drop out due to a non-hypertension related elective hospitalization, which resulted in a missed follow-up visit. Another patient missed visit at week 6. Figure 1 represents a flowchart of the study. Before BAT implantation, office BP was 160 ± 17/86 ± 11 mmHg, ABPM showed 150 ± 13/80 ± 9 mmHg for the 24 h average, 153 ± 13/83 ± 9 mmHg for the daytime and 147 ± 16/77 ± 10 mmHg for the nighttime measurement.

TABLE 1 Baseline characteristics

Parameter	$N = 24$
Male *n* (%)	18 (75%)
Female *n* (%)	6 (25%)
Age (years)	66 ± 9
BMI (kg/m^2)	33 ± 6
Prior renal denervation	4 (17%)
Relevant concomitant diseases	
Coronary heart disease *n* (%)	3 (13%)
Hyperlipoproteinemia *n* (%)	16 (67%)
BMI ≥30 kg/m^2 *n* (%)	16 (67%)
Diabetes mellitus *n* (%)	12 (50%)
Current smoker *n* (%)	2 (8%)
Chronic kidney disease ≥ CKD stage 3 *n* (%)	12 (50%)
CKD stage 5D *n* (%)	3 (13%)

Abbreviations: CKD, Chronic kidney disease; CKD stage 5D, Chronic kidney disease under renal replacement therapy.

Compared to pre-implant data, office BP ($p \leq .01/p \leq .01$) as well as all ABP parameters (24 h average $p = .01/p = .01$, daytime both $p < .01$, nighttime $p = .02/p = .04$) at baseline of the present study were significantly reduced (Table 2).

3.2 | Effects of BAT on nocturnal dipping

Percentage systolic dipping was 2 ± 6% at baseline with zero dippers (0%), but 16 non-dippers (70%), and 7 inverted dippers (30%). After a follow-up of 3 months with a two-step intensification of the nighttime BAT interval, the percentage systolic dipping significantly improved to 6 ± 8% ($p = .03$) and the dipping pattern changed to 6 dippers, 14 non-dippers, and 3 inverted dippers ($p = .02$, see Figure 2).

3.3 | Blood pressure, antihypertensive treatment, and safety

Systolic office ($p = .51$) and 24 h ambulatory BP ($p = .54$), 24-h heart rate ($p = .97$) as well as systolic day- ($p = .29$) and systolic nighttime ($p = .72$) ABP remained unchanged compared to baseline. The

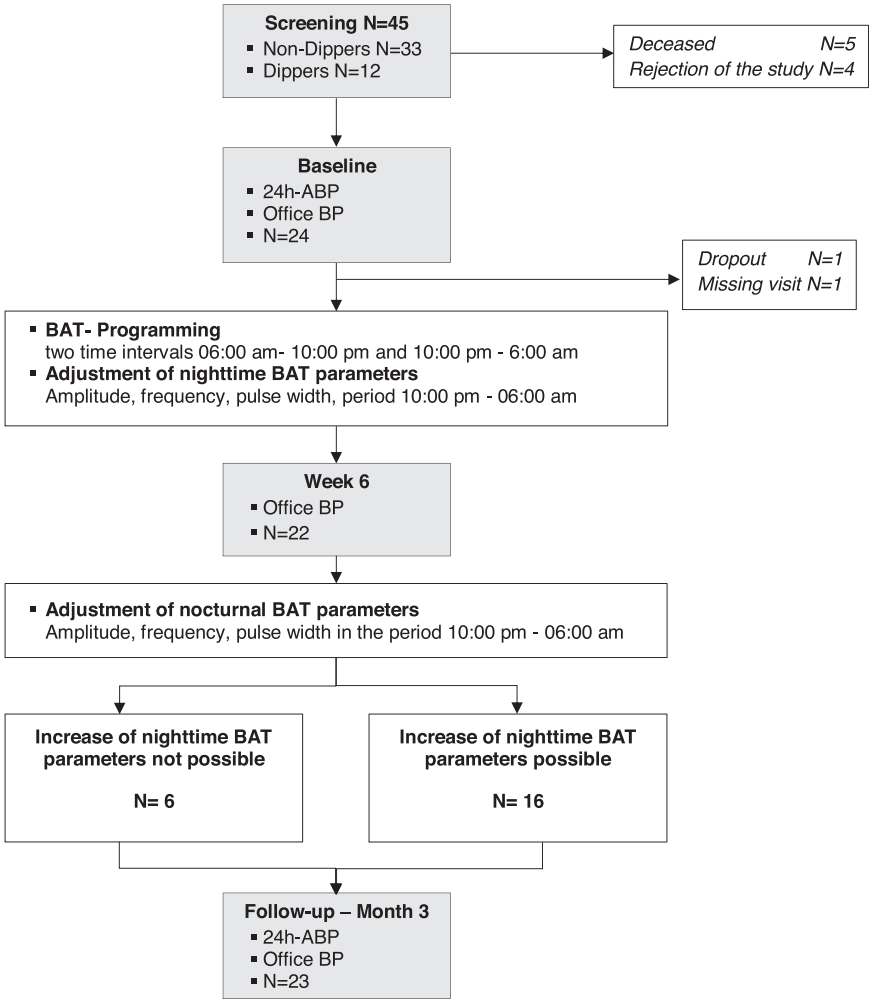

FIGURE 1 Flow chart of the study. Up-titration of nighttime BAT programming were performed in consideration of individual local side effects. Ambulatory blood pressure monitoring (ABP).

TABLE 2 Data on BP and antihypertensive treatment

Parameter	Baseline	Follow-up	*p*
Office BP (mmHg)	135 ± 22/72 ± 10	132 ± 18/73 ± 12	.38/.82
ABP – 24 h (mmHg)	135 ± 17/72 ± 10	137 ± 13/73 ± 10	.54/.61
ABP – daytime (mmHg)	135 ± 16/73 ± 11	139 ± 13/74 ± 10	.29/.51
ABP – nighttime (mmHg)	133 ± 20/70 ± 11	131 ± 16/68 ± 9	.72/.62
Systolic dipping (%)	2 ± 6	6 ± 8	.03
Diastolic dipping (%)	4 ± 8	7 ± 9	.10
Number of antihypertensive drugs	6.0 (IQR 4–9)	6.0 (IQR 4–9)	1.0
Number of nighttime antihypertensive drugs	2.0 (IQR 1–4)	2.0 (IQR 1–4)[a]	1.0

Values are mean ± SD, *n* (%), or median (range).
Abbreviations: ABP, ambulatory blood pressure; BP, Blood pressure.
[a]Dose de-/escalated in two patients each, respectively.

total number of prescribed antihypertensives kept unchanged with a median amount of 6 (IQR 4–9). Dosage of antihypertensives were stable, except for dose de-/escalated in two patients each, respectively. Median number of nighttime antihypertensives 2 (IQR 1–4) remained stable, as well. Within the different dipping classes, dippers took 2 (IQR 1–3) nighttime antihypertensives, non-dipper 2.5 (IQR 1–4) and the inverted dipper 4 (IQR 3–4). Data on BP and medication are summarized in Table 2. Solely mild, intermittent adverse events (AE) were detected. No change in the proportion of side effects was detected during follow-up. Baseline versus month 3 follow-up: paresthesia 7 (29%)

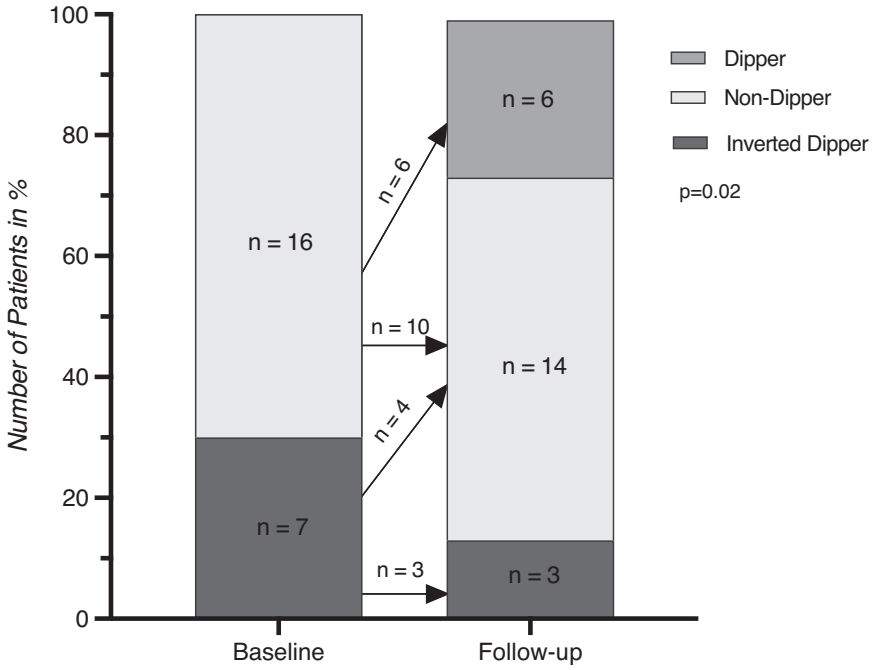

FIGURE 2 Dipping category at baseline and at follow-up after 3 months. Arrows depict the number of patients who changed categories.

TABLE 3 Programmed day- and nighttime parameters

Parameter	Baseline	Follow-up	*p*
Pulse width daytime (μs)	239 ± 166	242 ± 166	.06
Frequency daytime (Hz)	40 ± 10	40 ± 10	1.0
Amplitude daytime (mA)	5.8 ± 1.4	5.8 ± 1.3	.66
Pulse width nighttime (μs)	237 ± 161	267 ± 170	.003
Frequency nighttime (1/s)	40 ± 12	42 ± 10	.09
Amplitude nighttime (mA)	5.8 ± 1.3	5.8 ± 1.3	.95

Data are presented as mean ± SD.

versus 4 (17%) $p = .49$; intermittent dizziness 5 (21%) versus 1 (4%) $p = .19$; local muscle fasciculation 2 (8%) versus 0 (0%) $p = .48$; dysphagia 1 (4%) versus 0 (0%) ($p = 1.00$).

3.4 | BAT programming

Analysis of BAT parameters revealed a significant increase in nighttime pulse-width from 237 ± 161 to 267 ± 170 μs ($p = .003$) during follow-up, whereas daytime parameters as well as nighttime frequency and amplitude remained unchanged. Data on BAT-programming are summarized in Table 3.

3.5 | Comparison of responders and non-responders

A number of 11 patients (48%) showed an improvement of systolic dipping pattern after 3 months and were classified as responder to the intensification of nighttime BAT programming. Non-improvement or deterioration of the dipping profile was defined as non-response, which was detected in 12 patients (52%). There were no differences in characteristics between the responder and non-responder, except for gender distribution. A number of five out of six female participants (83%) were classified as responders (Table 4).

4 | DISCUSSION

This is the first study showing that programming of an intensified nocturnal BAT interval resulted in an improved nocturnal dipping and increased proportion of patients with favorable dipping profile in patients with resistant HTN. Nevertheless, overall BP level was not affected. Due to the high cardiovascular risk in patients with resistant HTN as well as in non-dippers a direct clinical relevance from the present findings.[27–31] In particular, SBP dipping, which was improved in the present study, seems to be an important cardiovascular indicator, especially for cerebrovascular infarctions.[32] Therefore, the achieved improvement in nocturnal dipping seems to be beneficial, although it was not accompanied by a relevant decrease in nighttime BP. A reduction in nocturnal BP by de novo BAT has already been shown by our study group.[33] It must be noted, that failure in further reduction of nighttime BP by intensification of nighttime interval BAT in the present study might be a result of the already occurred distinct BP reduction since initial BAT implantation (nocturnal SBP pre-implant 147 ± 16 mmHg vs. baseline 133 ± 20 mmHg, $p = .02$). The already reduced nighttime BP at study baseline might have interfered with further optimization of the nighttime BP. Though the present study investigated the effects of an intensification of nighttime BAT interval, the effects of de-novo BAT on dipping pattern would be of special interest. Whether intensified nocturnal BAT therapy contributes to a reduction in cardiovascular risk needs to be shown. As BAT offers the opportunity to

TABLE 4 Comparison of responders and non-responders

Parameter	Responder	Non-responder	*p*
N	11	12	-
Age (years)	65 ± 11	67 ± 8	.58
Female *n* (%)	5 (45%)	1 (8%)	.04
BMI (kg/m^2)	32 ± 6	34 ± 6	.48
Baseline 24 h ABP (mmHg)	140 ± 20/74 ± 10	129 ± 11/70 ± 10	.11/.28
Baseline nighttime ABP (mmHg)	139 ± 24/74 ± 12	126 ± 12/66 ± 9	.11/.10
Δ Daytime BP (mmHg) systolic/diastolic	+3 ± 27 /+2 ± 5	+9 ± 0 /+4 ± 7	.50/.73
Δ Nighttime BP (mmHg) systolic/diastolic	−15 ± 24 /−8 ± 13	+10 ± 9 /+5 ± 7	.03/.01
Systolic dipping at baseline (%)	1 ± 6	3 ± 6	.43
Number of antihypertensive drugs at baseline	5 (4–7)	9 (6–10)	.11
Number of nighttime antihypertensive drugs at baseline	2 (1–4)	4 (2–5)	.15
Hyperlipoproteinemia	8 (73%)	8 (67%)	.75
History of smoking	3 (27%)	7 (58%)	.10
Diabetes mellitus	4 (36%)	8 (67%)	.15
Chronic kidney disease ≥stage 3	7 (64%)	5 (42%)	.29
Former apoplexy	1 (9%)	4 (33%)	.16
Former myocardial infarction	0 (0%)	3 (25%)	.10

Data are presented as mean ± SD, median (IQR) and/or percentage (%). Delta (Δ) equals the change between month 3 and baseline.

modulate programming parameters in a differentiated manner, structured analysis of the effect of different BAT programming would be of interest for further studies. A prospective study also demonstrated that non-dipping is associated with microalbuminuria and is suggested to be a risk factor for progression of renal disease.[34] Therefore, it is fair to suppose, that changes in dipping status might have implications for end-organ damage. Accordingly, the improvement in BP dipping by nighttime BAT intensification of the present study is in accordance with results from previous studies, showing that BAT contributes to a reduction in albuminuria in patients with chronic kidney disease.[14]

In the present cohort 24 out of 36 potentially eligible patients (67%) treated with BAT could be initially classified as non- or inverted dipper. The high porportion of non- and inverted dipping in the present cohort is congruent with a prior study in resistant HTN showing a non- and inverted dipper rate of 65%.[35]

Previous studies already confirmed a significant BP lowering effect of BAT in patients with resistant HTN.[36] In the present study, nighttime intensification of BAT parameters resulted in a class change from non-dippers to dippers in six patients (26%). The present results are in accordance with reports investigating the effect of renal denervation on dipping status, which showed an improved dipping pattern as well.[21,37] However the largest study of renal denervation which investigated 346 patients did not show any improvement of dipping status.[38] In the present cohort four patients (17 %) had prior RDN. Prior experimental and clinical studies could demonstrate, that prior RDN did not abolish BAT effect.[10,39] Tough all of the patients included in the study showed non-dipping pattern at study baseline, an influence of prior RDN on the BAT effect on dipping pattern cannot fully be excluded.

Even more than class change from non-dipping to dipping, class change from inverted dipping to non-dipping, is of special. Inverted dipping is associated with increased neural activity, whereas there appears to be no difference between dippers and non-dippers in terms of sympathetic neural activity.[40] Thus, the observed class change from inverted dipping to non-dipping in four patients (17%), points to a reduction of sympathetic nervous overactivity. However, improvement of dipping status might serve as a potential marker of successful BAT treatment and suggests that BAT normalizes circadian rhythms and promotes the transition from non-dipper-status to dipper.

Several aspects have to be considered in the cause of the non-response in this study. First, patients analyzed in this study were not treated with BAT de novo, which might have already led to a prior shift to an improved dipping pattern in a proportion of patients. The patients showing non-dipping despite of prior BAT might therefore represent a pre-selected cohort of patients with potentially more pronounced dysregulation of the autonomic system. Second, the relatively common occurrence of local side effects during individual up-titration limited that the full potential of the therapy to improve the dipping pattern could be exploited. In particular, the comparison of baseline data revealed a lower 24 h and nighttime BP in non-responders indicating that those patients had already better BP control resulting in reduced scope for BAT escalation. This is in accordance with previous reports showing higher BP reduction in patients with higher baseline BP.[41] Of note, within the responder group, there were statistically significant more females compared to the non-responder group. This is particularly noteworthy, as gender differences in response to the sympathetic nervous system and the central control of sympatho-adrenal

functions have been described before.[42] The sympathetic nervous system in females appears to be less sensitive to excitatory stimuli and more sensitive to inhibitory stimuli compared with males.[42,43] Gender differences in arterial baroreflex sensitivity suggest that females may have an increased baroreflex sensitivity leading to a more extensive baroreflex reflex inhibition of sympathetic nerve activity and possibly resulting in an intensified renal excretory function.[42] Except for gender, there were no differences between characteristics between responders and non-responder. To further characterize potential differences between these groups measurement of the autonomic nervous system, such as muscle sympathetic nerve activity or heart rate variability would be of interest.

In non-dipper patients altered sympathovagal balance characterized by increased sympathetic and decreased parasympathetic nervous activity could be demonstrated compared to dippers.[44–46] Previous studies investigating parameters of the autonomic regulation (rate variability and heart rate turbulence) in patients with resistant HTN revealed that BAT modulate both actors of the autonomic nervous system leading to an inhibition of sympathetic activity and increase in parasympathetic activity.[5] Thus, BAT might be an interesting interventional approach to treat non-dipping in resistant HTN. However, as the study duration of 3 months is relatively short, it is unlikely that there was a structural improvement of autonomic neuropathy.

The present study has several important limitations. A major limitation is the small number of patients, which is the consequence of the current availability and diffusion of BAT in the treatment of resistant HTN. Therefore, the data should be interpreted with caution, especially with regard to the lack of significant changes. In fact, the present data might primarily serve for hypotheses generation. Larger studies need to confirm the presented results. The study is lacking randomization, a control group, and blinding. However, the apparently greater reduction in nighttime BP in non-dippers may be, at least in part, due to the effect of regression to the mean. A prospective, randomized, sham-controlled trial investigating BAT in patients with resistant hypertension using 24 h ABP with nocturnal dipping status as secondary endpoint could overcome the aforementioned limitations. Another relevant source for bias is the adherence to antihypertensive drugs. The present study did not assess the impact of adherence to antihypertensive medication. Changes in adherence might have influenced BP and dipping response throughout the study. Another limitation is, that no measures of indices of sympathetic activity, such as urinary catecholamines was performed within the study.

5 | CONCLUSION

Intensification of nighttime BAT programming may improve the dipping profile in patients with resistant hypertension, even if 24 h ABP is unchanged. The effect of de-novo BAT on dipping profiles need to be shown. The effect of nocturnal dipping improvement by BAT might be beneficial to reduce cardiovascular events, beyond the overall BP reduction effects of BAT.

AUTHOR CONTRIBUTIONS

MK and MW designed and supervised the study. Data collection was performed by EB, MW, MK, statistical analysis was done by EB, MW, AKS. MW, EB, and MK contributed to the interpretation of the data. Data visualization was conducted by EB. The original manuscript draft was prepared by MW and EB. The manuscript was reviewed and edited by MK, AKS, EB, MW. All authors read, agreed to, and approved the final version of the submitted manuscript.

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CONFLICTS OF INTEREST

MW and MK have received speaking honoraria and research grant from CVRx. MK is member of the CVRx Barostim Hypertension Registry Steering Committee. EB and AKS declare no conflict of interest.

PATIENT CONSENT STATEMENT

All patients provided informed consent before the initiation of the protocol-mandated procedures.

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