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Impact of medication adherence on the efficacy of Baroreflex activation therapy

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Abstract

Therapy adherence significantly determines the success of antihypertensive therapy, especially in patients with resistant hypertension. Our study investigates the impact of drug adherence on the efficacy of Baroreflex-activation-therapy (BAT). In this retrospective analysis, the authors measured blood pressure (BP) and antihypertensive medication adherence (by gas chromatography-mass spectrometry [GC-MS] urine analysis) before and 6 months after BAT initiation. Adherence was defined as detection of $\geq$80% intake of prescribed medication at the time of follow-up. Response to BAT was defined as BP drop $\geq$5 mmHg in systolic 24 h-ambulatory BP (ABP) after 6 months. Overall patients ($n = 38$) median medication adherence was low, but rose from 60% (IQR 25%–100%) to 75% (IQR 38%–100%; $p = .0194$). After 6 months of BAT, mean systolic and diastolic office BP (-21 $\pm$ 25 mmHg and -9 $\pm$ 15 mmHg; $p < .0001$ and .0004) as well as 24 h-ABP dropped significantly (-9 $\pm$ 17 mmHg and -5 $\pm$ 12 mmHg; $p = .0049$ and .0280). After 6 months of BAT, 21 patients (60%) could be classified as responders. There was neither significant difference in mean office systolic (-21 $\pm$ 23 mmHg vs. -21 $\pm$ 28 mmHg; $p = .9581$) nor in 24 h-systolic ABP decrease (-11 $\pm$ 19 mmHg vs. -7 $\pm$ 15 mmHg; $p = .4450$) comparing adherent and non-adherent patients. Whereas Antihypertensive Therapeutic Index (ATI) was unchanged in non-responders, it significantly decreased in responders (from 50 $\pm$ 16 to 46 $\pm$ 16; $p = .0477$). These data are the first to show that BAT-initiation leads to a clear BP reduction independently of patients' medication adherence. Response to BAT is associated with a significant lowering of ATI, which might contribute to an underestimation of BAT efficacy.

KEYWORDS
adherence, antihypertensive therapy, Baroreflex-activation-therapy, resistant hypertension, uncontrolled hypertension

1 | INTRODUCTION

Although Baroreflex-activation-therapy (BAT) is already approved in the EU in patients with therapy-resistant hypertension (HTN) and uncontrolled blood pressure (BP) ≥140/90 mmHg despite a triple antihypertensive therapy (including a diuretic) in maximal or maximally tolerated dose, in daily practice it is mostly applied to patients with therapy-refractory HTN, who take a combination of five or more antihypertensives.[1] For BAT, organ protective effects on vasculature and kidneys were shown in addition to a significant reduction of BP in office and ambulatory measurements.[1–4]

In addition to the exclusion of secondary forms of HTN, before BAT implantation adherence testing is recommendable,[5,6] since many hypertensive patients, who are difficult to treat, exhibit a high degree of non-adherence.[7,8] The problem in everyday life, however, is that simply asking patients about this topic is usually not helpful, and the guidelines do not recommend a defined method that can be objectified.[6] In clinical practice, in addition to BP control, the desire for less medication is a highly prevalent motivation for many patients to decide for BAT. However, it is an essential task for the treating physician to repeatedly explain to patients the necessity of optimal BP control and thus to guarantee adherence to pharmacological therapy. Nevertheless, a considerable number of hypertensive patients themselves reduce or stop their medication for various reasons.[9,10] Data on antihypertensive treatment persistence in BAT patients are rare. Initial adherence, as well as persistence to antihypertensive therapy, was not a subject of investigation in the BAT pivotal trial.[11] In a previous study we investigated antihypertensive medication adherence in a cohort of patients with apparently resistant hypertension, partially with regard to their eligibility for BAT, proving medication adherence to be of high relevance considering BP control.[7] Our current study summarizes the results of a retrospective evaluation of effects of adherence and persistence to antihypertensive drug therapy on the efficacy of BAT.

2 | METHODS

2.1 | Study design, evaluated parameters and ethical vote

In this retrospective study, we analyzed BP, antihypertensive medication and antihypertensive medication adherence in 38 patients suffering therapy-resistant arterial HTN, receiving a baroreceptor stimulator for antihypertensive treatment in the certified hypertension clinic of the University Medical Centre Göttingen from 06/2012 to 08/2016. Data were collected before BAT implantation (=baseline) and 6 months afterwards. Evaluated parameters were sex, age, body mass index (BMI), history of smoking, office and ambulatory BP (ABP), number of prescribed antihypertensive drugs, Antihypertensive Therapeutic Index (ATI) and antihypertensive medication adherence.

ATI was defined as the sum of the ratios of the prescribed dose of an antihypertensive drug to the maximum dose of this antihypertensive. After addition, the sum of ratios was multiplied by ten:

$$ATI = \left[\left(\frac{\text{dose of antihypertensive drug 1}}{\text{maximum dose of antihypertensive drug 1}} \right. \right.$$
$$+ \frac{\text{dose of antihypertensive drug 2}}{\text{maximum dose of antihypertensive drug 2}}$$
$$\left. \left. + \frac{\text{dose of antihypertensive drug } n}{\text{maximum dose of antihypertensive drug } n} \right) \times 10 \right]$$

The study was approved by the local ethics committee (# 19/9/11).

2.2 | BP measurement and therapy response

Initially, for office reading we measured BP on both upper arms. The arm with the higher value was used for all following measurements. Subsequently, BP was measured twice within a 3-min interval by a physician or study nurse, using a semiautomatic oscillometric device (Bosch und Sohn GmbH u. Co. KG, Jungingen, Germany) after 10 min of patientt's rest. The results of the two readings were averaged.

24 h-ABP was investigated using an oscillometric Spacelabs Model 90207 Recorder (Spacelabs Health care GmbH, Nürnberg, Germany) with measurements every 15 min during daytime and every 30 min at night. Readings were averaged after 24 h.

Based on the accepted cut-off for response to renal denervation, responders to BAT were defined as patients with ≥5 mmHg fall in systolic 24 h-ABP after 6 months of BAT.[12] Patients with no or less BP reduction were classified as non-responders.

2.3 | Detection and definition of adherence

Patientst' adherence to antihypertensive medication was measured by gas chromatography-mass spectrometry (GC-MS) urine analysis by the toxicological laboratory of the University Medical Centre Göttingen. Analyzed substances were Clonidine, Urapidil, Enalapril, Ramipril, Perindopril, Canrenone, Eplerenone, Spironolactone, Aliskiren, Irbesartan, Losartan, Valsartan, Bisoprolol, Metoprolol, Atenolol, Amlodipine, Lercanidipine, Nitrendipine, Nifedipine, Verapamil, Minoxidil, Hydrochlorothiazide, Furosemide, Torasemide, Indapamide, Piretanide, Xipamide and Chlortalidone. The GC-MS urine analysis only allows a qualitative statement of drug detection without further quantification of drug levels or detection of an irregular medication intake.

Patients were informed about the possibility of adherence measurements, but were unaware of the timing. Medication adherence was expressed as percentage of the ratio of detected to prescribed antihypertensive drugs. Patients were classified as adherent, if ≥80% of intake of prescribed medication could be detected at the time of follow-up at 6 months after baroreceptor stimulator activation. Patients with less medication intake were defined as non-adherent.

TABLE 1 Baseline characteristics

Baseline characteristics	All patients ($n = 38$)
Sex male/female (n)	20/18
Age (years)[a]	58 ± 12
BMI (kg/m^2)[a]	34 ± 6
History of smoking (%)	66
Office SBP (mmHg)[a]	169 ± 28
Office DBP (mmHg)[a]	91 ± 19
24 h-mean ABP (mmHg)[a]	108 ± 11
24 h-systolic ABP (mmHg)[a]	151 ± 14
24 h-diastolic ABP (mmHg)[a]	84 ± 12
Amount of prescribed antihypertensive drugs[a]	6 ± 2
ATI[a]	50 ± 13

Abbreviations: ABP, ambulatory blood pressure; ATI, antihypertensive therapeutic index, defined as the sum of the ratios of the prescribed doses of antihypertensive drugs to the maximum doses of these antihypertensives multiplied by ten; BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure.

[a]Values are expressed as mean $\pm$ standard deviation.

2.4 | Statistics

Data analysis was performed using the statistical software Graph-Pad Prism 5 and Microsoft Excel 2010. The D'Agostino and Pearson omnibus normality test was used to test data for normal distribution. Differences in the investigated variables on different time points were investigated using the paired t-test or Wilcoxon-signed-rank-test. Distinctions between different patient groups were analyzed using the unpaired t-test or Mann-Whitney test. Correlation analysis was performed by the Pearsont's correlation. Adherence is expressed as median and interquartile range (IQR), the other results are expressed as mean value $\pm$ standard deviation (SD). The threshold for statistical significance was chosen to be $p < .05$.

3 | RESULTS

3.1 | Baseline characteristics

At baseline, patientst' average age was 58 ± 12 years, 53% were male, mean BMI was 34 ± 6 kg/m^2 and 66% of patients had a history of smoking. Baseline mean office systolic BP (SBP) was 169 ± 28 mmHg, mean office diastolic BP (DBP) was 91 ± 19 mmHg. Mean 24 h-SBP was 151 ± 14 mmHg, average 24 h-DBP was 84 ± 12 mmHg. On average 6 ± 2 antihypertensive drugs were prescribed, mean ATI was 50 ± 13. Detailed baseline characteristics are shown in Table 1.

3.2 | Development of BP, antihypertensive medication and medication adherence

After 6 months of BAT, over all patients ($n = 38$) mean office SBP and DBP decreased significantly from 169 ± 28 to 148 ± 29 mmHg

($p < .0001$) and from 91 ± 19 to 82 ± 19 mmHg ($p = .0004$), respectively.

As well mean systolic and diastolic 24 h-ABP ($n = 35$) dropped clearly. Thereby mean 24 h-ABP declined from 108 ± 11 to 102 ± 19 mmHg ($p = .0120$), 24 h-SBP decreased from 151 ± 14 to 142 ± 23 mmHg ($p = .0049$) and 24 h-DBP decreased from 84 ± 12 to 79 ± 16 mmHg ($p = .0280$, see Table 2).

Simultaneously, overall patients median adherence to antihypertensive medication rose from 60% (IQR 25%–100%) to 75% (IQR 38%–100%; $p = .0194$). The raising adherence was accompanied by a stable amount of prescribed antihypertensives (6 ± 2 before and 6 ± 1 after initiation of BAT) but a falling ATI. ATI dropped significantly from 50 ± 13 to 47 ± 14 ($p = .0211$). Detailed data of medication, divided into adherent and non-adherent patients, are demonstrated in Table 2. Differentiated analysis of individual development of adherence rates and the proportion of specific adherence rates at baseline and after 6 months are shown in Figure 1.

Regarding the influence of patientst' adherence on BP development, patientst' BP in dependence to adherence state was analyzed. At this, adherent patients ($n = 18$) showed a clear reduction in office SBP and DBP ($p = .0012$ and $.0040$ respective), as well as a significant decline in systolic ABP ($p = .0369$) after 6 months of BAT. Reduction in mean and diastolic ABP barely missed the level of significance (see Table 2). Furthermore, in adherent patients, ATI dropped significantly from 54 ± 13 to 50 ± 11 ($p = .0261$), while the mean amount of prescribed antihypertensive drugs kept stable (see Table 2).

In non-adherent patients ($n = 20$) the decrease in mean office SBP from 170 ± 32 to 149 ± 35 mmHg and mean office DBP from 95 ± 21 to 88 ± 21 reached statistical significance ($p = .0057$ and $.0398$ respective). Mean, systolic and diastolic 24 h-ABP were numerically lower after 6 months of BAT as well (see Table 2).

In the comparison of the BP change in adherent and non-adherent patients, no significant differences in the BP development after 6 months of BAT could be seen in both patient groups, with falling BP values in adherent as well as non-adherent patients (Table 2). At the same time, adherence rate was not correlated with the extent of BP drop.

The influence of changes in adherence rate to the extent of BP drop is visualized in Figure 2. Although patients with stable or increasing adherence showed a higher fall in BP than patients with decreasing adherence rate, these differences did not reach statistical significance (see Table 3).

Also the other way round, no significant distinctions in the adherence rates of BAT-responders and non-responders could be found at baseline and after 6 months of BAT ($p = .5157$ for baseline adherence and $p = .4030$ for adherence at 6 months) with generally raising adherence rates in both patient groups after 6 months of baroreceptor implantation (see Table 4).

Thereby mean amount of prescribed antihypertensive drugs was similar at baseline in BAT-responders and -non-responders and showed no significant differences after 6 months. Differently, in BAT-responders mean ATI was lowered significantly from 50 ± 16 to 46 ± 16 ($p = .0477$), while ATI stayed stable in non-responders (see Table 4).

TABLE 2 BP and medication development of all, adherent and non-adherent patients after 6 months of BAT

B	All patients (n = 38)				Adherent patients (n = 18)				Non-adherent patients (=20)				p-Value delta adherent vs. non-adherent patients
	Baseline	6 months BAT	Delta	p-Value	Baseline	6 months BAT	Delta	p-Value	Baseline	6 months BAT	Delta	p-Value	
Office SBP (mmHg)	169.2 ± 27.5	148.2 ± 29.3	-21.0 ± 25.1	<.0001	167.9 ± 22.1	147.1 ± 22.1	-20.8 ± 22.7	.0012	170.4 ± 32.2	149.2 ± 35.1	-21.2 ± 27.7	.0057	.9581
Office DBP (mmHg)	90.7 ± 19.1	81.5 ± 18.6	-9.2 ± 14.6	.0004	85.5 ± 15.5	74.3 ± 13.2	-11.1 ± 14.2	.0040	95.4 ± 21.1	88.0 ± 20.7	-7.4 ± 15.0	.0398	.4367
24 h-Mean													
ABP (mmHg)	108.1 ± 11.2	101.5 ± 18.7	-6.5 ± 15.3	.0120	105.5 ± 8.1	96.9 ± 14.2	-8.3 ± 16.0	.0552	109.3 ± 13.7	105.4 ± 21.3	-5.1 ± 15.1	.1604	.5401
24 h-SBP													
(mmHg)	150.5 ± 14.4	141.9 ± 23.3	-8.6 ± 16.9	.0049	149.8 ± 9.3	138.0 ± 16.2	-11.0 ± 19.3	.0369	150.2 ± 18.9	145.2 ± 28.0	-6.6 ± 14.9	.0712	.4450
24 h-DBP													
(mmHg)	84.1 ± 11.6	78.8 ± 16.2	-5.3 ± 12.3	.0280	79.5 ± 9.1	74.3 ± 12.8	-5.6 ± 13.4	.1134	86.6 ± 13.0	82.6 ± 18.0	-5.1 ± 11.7	.0754	.8935
Amount of antihyper-tensives	6.4 ± 1.5	6.2 ± 1.4		.3370	6.3 ± 1.5	6.3 ± 1.4		.7903	6.4 ± 1.6	6.2 ± 1.5		.3299	
ATI	50.0 ± 13.4	46.8 ± 13.6		.0211	54.3 ± 12.9	49.5 ± 11.0		.0261	46.2 ± 13.0	44.4 ± 15.4		.3263	

Notes: Values are expressed as mean ± standard deviation. Patients were classified as adherent, if ≥80% of intake of prescribed medication could be detected at the time of follow up at 6 months after BAT activation. Otherwise they were classified as non-adherent.

Abbreviations: ABP, ambulatory blood pressure; ATI, antihypertensive therapeutic index, defined as the sum of the ratios of the prescribed doses of antihypertensive drugs to the maximum doses of these antihypertensives multiplied by ten; BAT, Baroreflex activation therapy; DBP, diastolic blood pressure; SBP, systolic blood pressure.
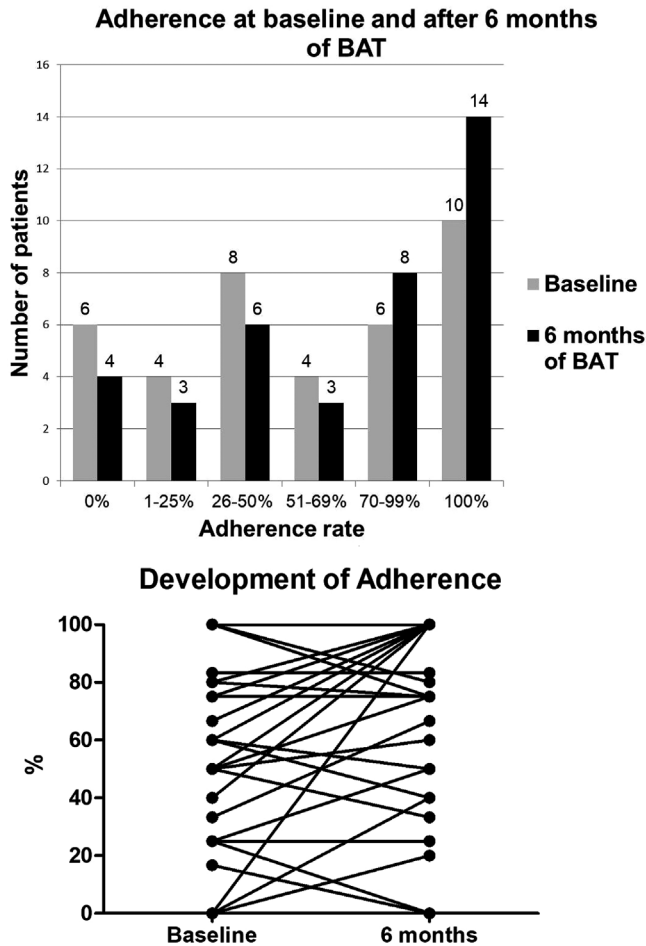
Adherence at baseline and after 6 months of BAT

Development of Adherence

FIGURE 1 Development of adherence rates of all patients after BAT implantation. BAT, Baroreflex activation therapy

4 | DISCUSSION

BAT was proven to be a safe and efficient treatment option for patients with therapy-resistant hypertension.[1,13] Other studies have highlighted the crucial role of medication adherence for BP control and have shown that non-adherence plays an important role in patients with apparently resistant hypertension.[8,14–16] In a previous study our group investigated antihypertensive medication adherence in a cohort of patients with apparently resistant hypertension as well, proving non-adherence to be a relevant issue in relation to the treatment of these patients and in regards to interventional treatment options.[7] De Jager and colleagues analyzed the influence of medication adherence on the effect of renal denervation, showing generally low adherence rates in patients undergoing this treatment option.[17] However changing adherence rates over time make it difficult to evaluate the real BP-lowering effect of renal denervation[17] and interventional treatment options in general. In the current investigation, we retrospectively analyzed BP and adherence development before and 6 months after initiation of BAT, looking at the impact of medication adherence on the efficacy of BAT.

Retrospective data analysis from a single center as well as the applied method for adherence measurement cause some limitations to our study. The method used only allowed a yes/no statement of drug detection without further differentiation of an erratic drug intake or quantification of individual drug levels. As well substances as Lisinopril, Candesartan, Telmisartan, Doxazosin or Moxonidine were not traceable. Despite that, this study is the first to examine adherence rates after BAT implantation and objective adherence measurement seems to deliver more reliable results than other measuring methods (e.g., questionnaires), as detected adherence rates show a close dependence of the applied measurement method.[10] In our study patients were informed about the possibility of adherence measurement, but were unaware of the timing since urine probes were collected on different time points and as well for other reasons than adherence testing. Nevertheless, the knowledge about the potential adherence testing might have influenced drug intake. Furthermore, the adherence rate measured in this study might be overestimated, using the very sensitive GC-MS urine analysis for adherence assessment, whereby already past or sporadic drug intake could lead to the detection of the substance.

After 6 months of BAT, the significant drop of mean systolic and diastolic office and ABP as well as the considerable fall in ATI imply a distinct antihypertensive efficacy of BAT. Though, after 6 months of therapy initiation patients' adherence rate to antihypertensive medication was also significantly improved, so direct conclusions on the antihypertensive effect of BAT and the interference of BAT and medication adherence are difficult.

Therefore, we separately analyzed the BP development for adherent and non-adherent patients and undertook a correlation analysis between adherence rate and BP development to differentiate between the effect of BAT and the impact of the raising adherence. Thereby no significant differences in the BP changes after 6 months of BAT could be seen comparing adherent and non-adherent patients. At the same time, adherence rate was not correlated with the extent of BP drop. Furthermore, no statistical significant differences in the BP development of patients with stable, increasing or decreasing adherence rate could be determined, confirming the independent antihypertensive efficacy of BAT. This is further supported by the fact that no significant distinctions in the adherence rates of BAT-responders and -non-responders could be found at baseline and after 6 months of therapy.

Additionally, we undertook a differentiated analysis of the groups of BAT-responders and non-responders. Based on the accepted cut-off for response to renal denervation, response to BAT was defined as BP drop ≥5 mmHg in systolic 24 h-ABP after 6 months of BAT.[12] Response to BAT led to a significant decrease of ATI, while it stayed stable in non-responders. This reduction of ATI reveals an adequate adaption of medication to the lowered BP, but might result in an underestimation of the BAT effect on BP in the present study. So, further investigations in adherent patients with a constant medication intake are needed to evaluate the true BP effect of BAT. Moreover, the decreasing ATI, reflecting a reduced dosing of antihypertensive medication, indicates two important consequences of interventional BP treatment; *the possibility* and *the requirement* to adapt antihypertensive
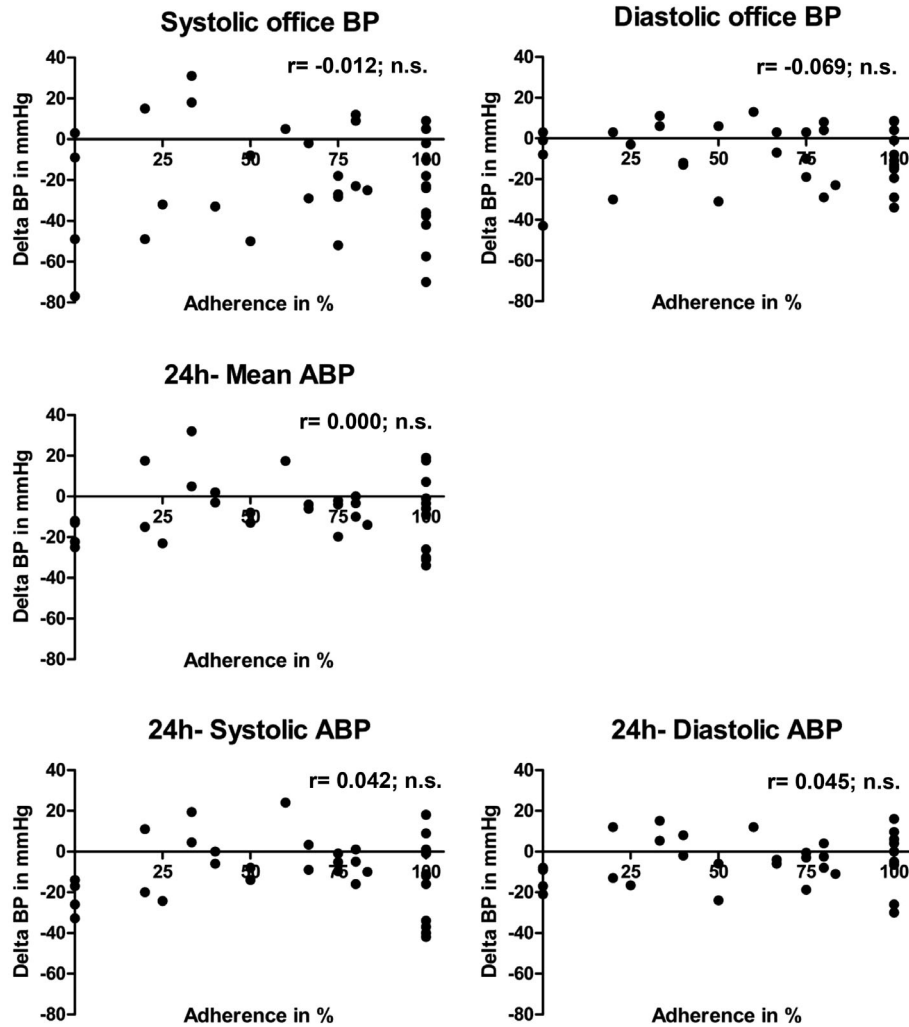
FIGURE 2 BP change in dependency of adherence rate. ABP, ambulatory blood pressure; BP, blood pressure in mmHg; r, correlation coefficient; n.s., not significant

medication after interventional therapy initiation. Though the number of prescribed medication remained stable in our study, the reduced ATI may indicate the possibility to reduce medication also numerically over time. Less medication in turn often results in an improved patient comfort and adherence.[9,14] The other way round physicians must be aware of the possible need for reduction of medication to prevent potential hypotension. So, one possible reason for non-adherence in BAT-responders could be hypotension due to efficient BP reduction. In our study, 12 patients who respond to BAT showed non-adherence. Thereby ten patients showed non-adherence already before initiation of BAT and from the six patients who showed a decreasing adherence, only one had a systolic 24 h-ABP <120 mmHg (namely 117 mmHg). So, hypotension seems not to be the main reason for non-adherence in BAT-responders.

As mentioned above, low medication adherence is a huge and relevant problem in patients with uncontrolled BP and those, who are considered for interventional treatment options[14,15,17,18] and was a documented phenomenon in our investigation, too. Since adherence analysis was performed mostly independent from eligibility analysis for

TABLE 3 Extend of BP drop after 6 months of BAT in patients with a stable, increasing or decreasing adherence rate

	Stable adherence (n = 11)	Increasing adherence (n = 16)	Decreasing adherence (n = 11)
Delta office SBP	-19 ± 18	-26 ± 25	-16 ± 32
Delta office DBP	-11 ± 12	-9 ± 15	-7 ± 18
Delta 24 h-mean ABP	-8 ± 14	-7 ± 18	-4 ± 15
Delta 24 h-SBP	-10 ± 16	-9 ± 22	-7 ± 13
Delta 24 h-DBP	-5 ± 9	-7 ± 16	-4 ± 10

Notes: Values are expressed as mean ± standard deviation.
Abbreviations: ABP, ambulatory blood pressure; BAT, Baroreflex activation therapy; BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

BAT, some non-adherent patients were treated with BAT as well. In consideration of the present data, in future, there should be a greater focus on patientsť drug intake and adherence-improving methods prior to BAT implantation.

TABLE 4 Adherence, amount of prescribed antihypertensive drugs and ATI in BAT-responders and –non-responders at baseline and after 6 months

	Adherence (%)			Amount of antihypertensives (n)			ATI		
	Baseline	6 months BAT	p-Value	Baseline	6 months BAT	p-Value	Baseline	6 months BAT	p-Value
Responder (n = 21)	60.0 (20.9–91.7)	75.0 (22.5–100)	.2557	6.4 ± 1.6	6.0 ± 1.7	.1036	50.1 ± 15.8	45.7 ± 15.6	.0477
Non-responder (n = 14)	55.0 (38.3–100)	77.5 (38.3–100)	.1992	6.4 ± 1.3	6.4 ± .9	1.0000	50.3 ± 9.1	48.4 ± 10.6	.3078

Note: Adherence is expressed as median and interquartile range, other values are expressed as mean ± standard deviation. BAT – Baroreflex Activation Therapy. BP – Blood pressure. Responders to BAT were defined as patients with ≥ 5 mmHg fall in systolic 24 h-BP after 6 months of BAT. Patients with no or less BP reduction were classified as non-responders.

Low adherence is associated with an increasing cardiovascular risk.[19,20] So, the sometimes clearly improved adherence after BAT implantation can be considered as an additional positive side effect of this therapy option. Though it is not particular for BAT, as the effect of an improving adherence could be seen in patients undergoing renal denervation as well.[17] This, however, might be in part responsible for the well-known Hawthorne effect, which occurs in BP intervention studies using interventional devices. Generally, an intensified patient-physician interaction was shown to yield in an increasing patientsť adherence.[9,10] Therefore, it could not be rule out that the intensified patient-physician interaction within the BAT evaluation and therapy monitoring has resulted in an improved medication adherence.

Beyond that, our data demonstrate that BAT-initiation leads to a clear BP reduction additionally and independently of this improvement of patientsť adherence.

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CONFLICTS OF INTEREST

Manuel Wallbach and Michael J. Koziolek have received speaking grant from CVRx. Michael J. Koziolek is member of the CVRx Barostim Hypertension Registry Steering Committee. Ann-Kathrin C. Schäfer, Dieter Müller, Ellen Born, Maria Mühlhaus, and Stephan Lüders have no conflicts of interest.

AUTHOR CONTRIBUTIONS

Manuel Wallbach and Michael J. Koziolek designed and supervised the study and undertook the clinical investigation. Data collection was performed by Ann-Kathrin C. Schäfer, Dieter Müller, Ellen Born and Maria Mühlhaus, statistical analysis was done by Ann-Kathrin C. Schäfer. Ann-Kathrin C. Schäfer, Dieter Müller, Ellen Born, Maria Mühlhaus, Stephan Lüders, Manuel Wallbach and Michael J. Koziolek contributed to the interpretation of data. Data visualisation was conducted by Ann-Kathrin C. Schäfer. The original manuscript draft was prepared by Ann-Kathrin C. Schäfer. The manuscript was reviewed and edited by Ann-Kathrin C. Schäfer, Dieter Müller, Ellen Born, Maria Mühlhaus, Stephan Lüders, Manuel Wallbach and Michael J. Koziolek.

All authors read, agreed to and approved the final version of the submitted manuscript.

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