Journal of Human Hypertension (2009) 23, 325–331

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ORIGINAL ARTICLE

Treating hypertension in type II diabetic patients with device-guided breathing: a randomized controlled trial

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The objective of the study was to evaluate the efficacy of device-guided breathing to lower blood pressure (BP) in hypertensive type II diabetic patients. A randomized controlled trial was carried out in four urban family practice clinics in Israel. Non-insulin-dependent diabetic, hypertensive patients with uncontrolled BP, receiving antihypertensive therapy or those non-medicated were enrolled. Baseline characteristics of the 66 patients who completed the study (33 intervention and 33 control) were: 62% men, age 62 ± 8 years (mean ± s.d.); body mass index 29 ± 5 kg/m²; systolic BP 148 ± 11 mm Hg and diastolic BP 81 ± 9 mm Hg. The intervention group used a device (RESPeRATE), which interactively guides the user towards slow and regular breathing by synchronizing respiration voluntarily to musical tones for 15 min daily for an 8-week period. The control group continued with their regular treatment. BP was measured in the clinic at baseline, after 4 weeks and at 8 weeks. Medication was unchanged for 4 weeks prior to and during the study period. The main outcome measure was the office BP change from baseline to the end of the 8-week period. BP was reduced in the treatment group (mean ± s.e.) systolic −10.0 ± 1.8 mm Hg and diastolic −3.6 ± 1.3 mm Hg ($P<0.0001$ and $P<0.01$), but not in the controls +1.6 ± 2.1 and −1.0 ± 1.4 mm Hg $P>0.4$ and $P>0.4$, respectively. Test for between group difference $P<0.0001$ and $P=0.08$. The subjects were highly compliant with the treatment, performing 75% of the requested exercise sessions. Greater BP reduction was observed with increased compliance with device usage ($P=0.01$ and $P=0.001$). It is concluded that self-treatment with device-guided breathing at home for 8 weeks by non-insulin-dependent diabetic patients was associated with a substantial reduction in office systolic BP.
Journal of Human Hypertension (2009) **23,** 325–331; doi:10.1038/jhh.2008.135; published online 13 November 2008

Keywords: type II diabetes mellitus; blood pressure; non-pharmacological therapy; paced breathing; RESPeRATE

Introduction

Hypertension is a common comorbidity in patients with diabetes mellitus being approximately twice as prevalent as in a non-diabetic population.[1,2] Epidemiological evidence has shown that hypertension is an important factor in the increased risk of coronary heart disease and stroke in subjects with diabetes. Mortality among diabetic patients increases with elevation of both systolic and diastolic BP.[3] It has been estimated that a high percentage of diabetic complications can be attributed to hypertension.[4] In diabetic patients, hypertension may also promote the development of microvascular complications such as retinopathy[5] and nephropathy.[6] Hypertension and diabetes should therefore be diagnosed and treated early and aggressively.[7]

Treatment should include pharmacological and non-pharmacological interventions to reduce blood pressure (BP) below 130/80 mm Hg.[8–10] Clinical trials have demonstrated the benefit of lowering BP in diabetic patients.[11,12] However, data show that only 44.3% achieve a BP <140/90 mm Hg and only 20.4% reach the recommended target of <130/80 mm Hg.[13] Compliance with drug therapies is compromised by cost, high frequency of dosing and side effects.[14] Use of some antihypertensive medication may even precipitate the clinical onset of diabetes,[15] making the use of non-pharmacological treatment even more attractive.

The efficacy and safety of reducing systolic BP in hypertensives by 15 min of daily paced breathing exercises, interactively guided by a device (RESPeRATE) in the home setting for 8 weeks, has been demonstrated in seven independent studies.[16–22] These studies consistently showed a reduction in systolic BP. However, diabetes mellitus was an

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Received 2 July 2008; revised 8 October 2008; accepted 9 October 2008; published online 13 November 2008

exclusion criterion in six out of the seven studies. This was done in an attempt to investigate the safety and efficacy of reducing BP in a homogenous population.

The objective of the present study was to evaluate the efficacy of device-guided breathing exercises in lowering BP in type II diabetic patients with uncontrolled BP, as an adjunct to usual care.

Materials and methods

The study was randomized and controlled with parallel design, including a two-visit baseline, a follow-up visit after 4 weeks and termination at the end of 8 weeks. Both the control and treatment groups continued their usual care, whereas the intervention group also performed daily device-guided breathing. To minimize the difference in the expectation of benefit, all patients were offered use of the treatment device, either immediately or after 8 weeks ('waiting list' type of control). The study hypothesis was that systolic BP would be reduced in the intervention group in patients who used the treatment device and that the reduction would be greater than that observed in the control group. A choice was made of 'usual care' as a control instead of an active control, for example a device that generates music as used in earlier studies,[16,17,23] as the latter could introduce a device-specific effect that prevents evaluation of the net device effect in 'real life', especially if such a device is not a validated therapeutic intervention.[24]

The study was approved by the Research Ethics Committee of the Hadassah-Hebrew University Medical Center.

Study population

After a clinic chart review, hypertensive diabetic patients from four urban family practices were invited to participate in the study. Inclusion criteria were: non-insulin-dependent diabetic subjects, a diagnosis of hypertension with a systolic BP above 130 mm Hg and/or a diastolic BP above 80 mm Hg on enrolment, unmedicated or not having changed pharmacological antihypertensive therapy, diet or exercise pattern for 1 month prior to enrolment, age 40–79 years and gave informed consent. In accord with earlier studies examining the use of this device in hypertensive patients, exclusion criteria were patients taking insulin, unstable ischaemic heart disease, stroke with major impairment, major organ failure, asthma, chronic respiratory disease, major psychiatric disorder, body mass index over 40 kg/m^2, pregnancy and major sight or hearing impairment that could hinder the use of the treatment device. Subjects with an average BP over 130/80 mm Hg were enrolled at the second of two baseline visits. If the difference in BP levels between the two visits was greater than 10 mm Hg for systolic BP or 5 mm Hg for the diastolic BP, the subject was invited for a third measurement and the average of three visits was used as the baseline. Written informed consent was obtained. Subjects who met the study criteria were randomized into intervention or control groups. To maintain equal-size groups in case of potential dropout, subjects who dropped out after randomization were automatically replaced by the next enrolled patient. Patients were recruited during a 2-year period starting in September 2004.

Interventions. Both the intervention and control groups continued their usual care, including pharmacological treatment, diet and physical exercise. Change in any of these parameters during the study was considered as a reason for stopping participation. In addition, the intervention group used a commercially available device for the treatment of hypertension (RESPeRATE; InterCure Ltd, Lod, Israel). The device interactively guides the user towards slow breathing with prolonged exhalation. The device consists of a control box containing a microprocessor, a belt-type respiration sensor and headphones to provide feedback to the patient. During a session of device-guided breathing, the device analyses the breathing rate and pattern and creates a personalized melody comprising two distinct tones, one for inhalation and one for exhalation. As the patient synchronizes inhalation and exhalation with the tones, the device gradually prolongs the exhalation tone and slows the breathing rate to less than 10 breaths per minute ('slow breathing'). A record of the patient's use of the device is stored in the microprocessor for assessment of total time of device use and breathing rate and pattern in 1-min intervals during the individual sessions.[20]

Data were collected at the family practice clinics and from information automatically stored by the microprocessor in the treatment device and were downloaded at the end of the study.

Study protocol. The intervention group received the RESPeRATE device in the clinic. They were given simple written instructions provided by the manufacturer about its use. The subjects were requested to use the device in a quiet room at home in the evening for 15 min daily for an 8-week period. They were instructed to attempt to accumulate at least 45 min of slow breathing, below 10 breaths per minute, per week. This measure of weekly effective exercise time appears on the display screen when the device is turned on. A help desk was available by phone to solve technical problems as part of the service routinely provided by the manufacturer to people who purchase the device.

Measurements and outcomes. The BP of all the study participants was measured by an experienced family physician using a mercury sphygmomanometer on the right arm, following the JNC-7

(Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure) recommendation.[8] Office BP values were the mean of the last two of three consecutive measurements taken 1 minute apart. BP measurements were taken at baseline, and after 4 and 8 weeks. The heart rate and BP measurements were taken at the same time for each individual patient, either in the morning or afternoon and were distanced from the device usage in the evening. The investigators were not blinded in the follow-up visits.

It was decided not to add home BP monitoring for both groups, as was done in earlier studies with the present device.[17–21] This procedure is known to have an effect on BP or compliance with other antihypertensive treatments.[25,26] Thus, the potential interaction between both factors (tested device and BP monitor) could bias evaluation of the study hypothesis, similar to that demonstrated by the antihypertensive effect of combined lifestyle modifications.[27]

Performance data stored by the device microprocessors were downloaded after the end of the study. The device usage was measured by the number of sessions performed and the total time spent in slow breathing, below 10 breaths per minute.

Data collected included demographic details, the duration of diabetes, comorbidity, medication status, participation in physical exercise, diet, smoking and drinking habits as well as the subjects' weight, height and heart rate. Fasting blood sugar, fructosamine and glycated haemoglobin (HbA_1c) were measured after enrolment and after 8 weeks and the presence or absence of microalbuminuria was noted.

The primary outcome measure was the systolic BP change, measured in the doctor's office at baseline and at termination after 8 weeks. Changes in diastolic BP, heart rate and measures of device usage were secondary outcomes.

Sample size. Sample size was determined by assuming a difference of 7.5 mm Hg systolic BP change between groups and a standard deviation of 12 mm Hg for the difference estimated from our earlier reported results.[16,20] Taking 80% as the power of the test and a one-tailed minimum significance level of 0.05, we obtained a minimum sample size of 64 patients.

Statistical analysis. The study hypothesis was tested by comparing the primary outcome separately for all randomized patients who had outcomes irrespective of compliance (intention to treat analysis). In an additional analysis, patients who dropped out were included.[28] Comparisons were made using *t*-test and analysis of variance with adjustment for contributing baseline characteristics, including BP. As this design involves a superiority comparison, a one-tail *P*-value is required,[29] that is, given two interventions A and B, a superiority comparison of response to A + B with response to A requires one-tail *P*-value, whereas a similarity comparison of A with B requires two tails. In our study, A represents usual care, whereas B represents device-guided breathing. In addition, the hypothesized systolic BP reduction in the treatment group was tested by comparing the primary outcome to zero (one-sample *t*-test). Comparisons by group of baseline characteristics were done by *t*-test for continuous variables and by Fisher's exact test for categorical variables. The device usage was compared with the requested administration of the treatment. Relationships between primary outcome and device usage were analysed by analysis of variance applied to performance parameters grouped in tertiles. All statistical analysis was performed using the SYSTAT7.0 software package (SPSS Inc., Chicago, IL, USA). Significance levels were $P<0.05$ (two-tail for similarity comparisons and one-tail for superiority comparisons).

Results

In total, 108 patients were invited to participate in the study. Thirty-four patients did not meet the study criteria, either because the BP was too low or the body mass index was too high. Three patients decided to discontinue participation after the first of two intake examinations. The remaining 71 were randomized into intervention and control groups. Five patients from the intervention group dropped out. One complained of mild dizziness at the 4-week visit and was requested to stop participation. Another patient had to change medication during the first week of the study due to large fluctuations in his BP. Three other patients who received the device did not use it at all and after 4 weeks stopped formal participation. These latter four patients therefore did not have BP measures at the end of the study. Baseline characteristics of the remaining 66 patients who participated throughout the duration of the trial, 33 treatment and 33 controls, are presented in Table 1. The antihypertensive medication status of the study population was as follows: 18% of the patients were unmedicated, 21% were taking one drug, 21% were taking two drugs, 21% were taking three drugs, 11% were taking four drugs and 8% were taking five drugs. The patients reported a relatively healthy lifestyle, including physical exercises (71%), diet (75%), not smoking (89%) and not consuming alcohol (85%). In total, 30% of the study population were born in Israel, 32% were born in Europe or America, 20% in Asia and 18% in North Africa, The mean number of years of education was 13 (range 6–20). The mean duration of diabetes was 6.6 years (range 1–23). There were no significant differences between the groups, including heart rate, fasting blood glucose, fructosamine and HbA_1c levels, and lifestyle ($P>0.05$).

Paced breathing effect on BP

As shown in Figure 1, treatment with device-guided breathing significantly reduced systolic BP

Table 1 Baseline demographic and clinical characteristics (mean ± s.d.)

Variables	*Treatment*	*Control*	P-*value*
n	33	33	
% men	20 (61%)	21 (64%)	1.00
Age (years)	62 ± 9	63 ± 8	0.74
BMI (kg/m²)	29 ± 6	30 ± 3	0.43
Taking antihypertensive medication	25 (76%)	29 (88%)	0.34
ACE inhibitor	20	23	1
Beta blocker	18	11	0.08
Calcium channel blocker	10	14	0.45
Diuretic	11	17	0.14
Alpha blocker	8	7	0.77
Taking antidiabetes medication	24 (73%)	20 (61%)	0.43
Systolic BP (mm Hg)	150 ± 12	147 ± 10	0.27
Diastolic BP (mm Hg)	81 ± 10	81 ± 8	0.98
Heart rate (b.p.m.)	70 ± 12	74 ± 10	0.21
Pulse pressure (mm Hg)	68 ± 14	65 ± 11	0.36
HbA_1c	7.7 ± 2.6	7.1 ± 1.3	0.09
Microalbuminuria	11 (33%)	11 (33%)	1.00

Abbreviations: ACE, Angiotensin-converting enzyme inhibitor; BMI, body mass index; BP, blood pressure; HbA_1c, glycated haemoglobin.

($P<0.0001$), diastolic BP ($P<0.01$) and pulse pressure ($P<0.0002$), whereas none of these variables was changed in the control group ($P>0.2$ for all). The difference in BP change (mean ± s.d.) between the treatment and control groups was significant for systolic BP -10.0 ± 10.5 vs $+1.6 \pm 12.3$ mm Hg, $P<0.0001$. Diastolic BP was not significantly changed -3.6 ± 7.3 vs -1.0 ± 8.0 mm Hg, $P=0.08$. Pulse pressure was also significantly reduced in the treatment group compared with the control -6.4 ± 8.6 vs $+2.6 \pm 12.8$ mm Hg, $P<0.001$. There was no significant change in the heart rate. As covariates, gender, age, medication status and other baseline characteristics were found to have no significant effect on the observed BP changes. When applying intention to treat analyses, the difference in BP changes between the treatment and control groups remained significant. The inclusion of the one patient in the treatment group who dropped out at 4 weeks and who had a BP measurement at that time gave a BP change of -9.5 ± 10.8 and -3.3 ± 7.5 mm Hg for the treatment group compared to $+1.6 \pm 10.8$ and -1.0 ± 8.0 mm Hg in the control group ($P=0.0001$ and $P=0.12$). The inclusion of all 71 randomized patients, conservatively undertaken by carrying on the baseline BP as the end value for the additional four patients who withdrew, gave a BP change of -8.5 ± 10.6 and -2.9 ± 7.1 mm Hg for the treatment group compared to $+1.4 \pm 12.4$ and -1.0 ± 8.0 mm Hg in the control group ($P=0.0002$ and $P=0.14$).

The results at the 4-week visit of the 34 patients in the treatment group and 31 patients in the control group (2 patients in the control group did not attend) show that the difference between the groups started to develop within 1 month of treatment. The 4-week BP change was -5.2 ± 13.9 and -2.4 ± 8.0 mm Hg for the treatment group compared to -0.7 ± 8.5 and -2.4 ± 4.8 mm Hg for the control ($P=0.06$ and $P=0.5$).

Systolic BP reduction was observed in 29/33 (88%) of the patients in the treatment group compared to 15/33 (45%) in the control group ($P<0.001$). BP control was better in the treatment group with the target of $<130/80$ mm Hg being reached by 27% of treated patients (9/33), compared to 6% (2/33) in the control group ($P=0.025$).

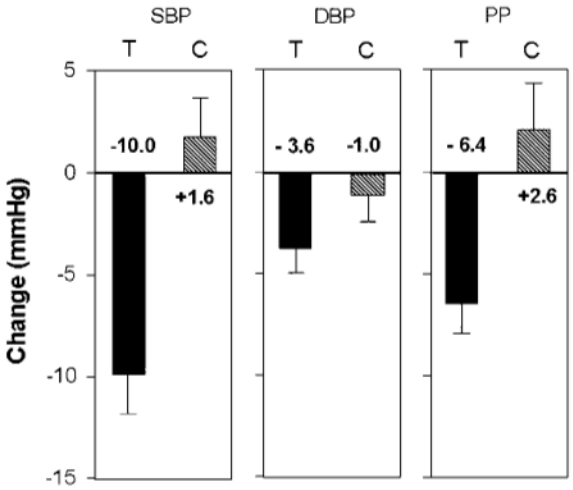

Figure 1 The mean change in systolic blood pressure (SBP), diastolic BP (DBP) and pulse pressure (PP) from baseline to the 8-week follow-up visit in the treatment (T) and control (C) groups. The significance of outcomes, by group, were $P<0.0001$, $P=0.08$ and $P<0.001$, from left to right, respectively. Error bars (s.e.) are marked.

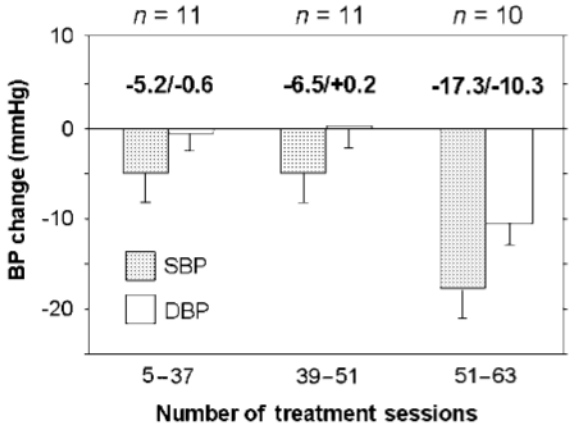

Figure 2 Dose–response relationship between device use (number of treatment sessions grouped by tertiles) and the blood pressure (BP) change adjusted to age and baseline BP level. One device was misplaced. Error bars (s.e.) are marked. The bars correspond to changes in systolic and diastolic BP, respectively, showing significant dependence on the number of treatment sessions ($P=0.01$ and $P=0.001$). Three patients with 51 treatment sessions were further subdivided by total time spent in device usage.

Dose–response relationship

Figure 2 shows that the more the time spent in performing breathing exercise, the greater the BP

reduction. The greatest BP reduction was achieved by the group that performed the highest number of sessions ($P=0.01$ and $P=0.001$).

Patient compliance with treatment
The subjects were highly compliant with the treatment and performed a mean of 42.1 ± 14.4 (range 5–63) of the requested daily exercise sessions (75%), during the 8-week study period. The mean session duration was 14.6 min of the 15 min requested (range 8.5–17.7). On average, 60% of the session time (range 19–100) was spent in slow breathing, less than 10 breaths per minute.

There were no significant changes in the fasting blood glucose, fructosamine or HbA_1c levels during the study. Neither was there an association between the presence of microalbuminuria as a marker of autonomic neuropathy[30,31] and the BP response to the use of the device. In addition, there was no correlation between duration of diabetes and BP response. Neither were there any differences between groups or change during the study in patient exercise, smoking, alcohol and diet habits.

Safety. The tested device carries few risks. Safety was assessed by reporting adverse events. Except for one patient with mild dizziness, whose participation in the study was stopped, no side effects were reported.

Discussion

Similar to findings in studies in non-diabetic hypertensive patient populations treated with device-guided breathing, our present study showed a significant reduction in systolic BP in a group of type II diabetic patients who performed guided breathing exercises at home for 15 min a day with the aid of the RESPeRATE device. The diastolic BP was not significantly reduced. This result could be expected as the baseline average diastolic BP was close to normal (mean 81 mm Hg), and the reduction rather small.[19,32] The same reasoning explains the significant reduction in the pulse pressure in response to the treatment. Greater BP reduction was observed in patients who performed more breathing exercise sessions.

Additional factors leading to BP elevation may be present in diabetic patients compared to non-diabetic hypertensive patients. The duration of the disease and the presence of target organ damage may reduce the possibility of its correction by non-pharmacological treatment. In our study, we found no correlation between the reduction of BP in the group using the device and duration of disease.

Slow and regular breathing, below 10 breaths per minute with prolonged exhalation, is known to activate, due to the increased tidal volume, pulmonary stretch receptors that affect reflex control of the cardiovascular system in a variety of ways. These include inhibition of sympathetic outflow during exhalation and arteriolar vasodilatation,[33–36] which may be of benefit to patients with hypertension and congestive heart failure.[37,38] This may not be the case in diabetic patients due to autonomic dysfunction.[39] Neuropathy, a common complication in diabetes, is caused by damage to the blood vessels that supply the nerve fibres and might be expected to reduce the benefit provided by the device. Moreover, the albumin excretion rate has been found to correlate with deteriorating autonomic function in diabetes, and is recognized as a reliable indicator of cardiovascular autonomic neuropathy.[30,31] However, no correlation between the presence of microalbuminuria and BP reduction with the aid of the device was found. We therefore suggest that the presence of neuropathy may not limit the use of the device in treating hypertensive diabetic patients. However, further research is needed to elucidate this question.

A potential limitation of our study was the lack of a longer follow-up period. In earlier studies, carried out on non-diabetic hypertensive patients under the same conditions, an 8-week follow-up period proved to be sufficient. However, in our present study, the finding that the main reduction of BP was generated towards the end of the treatment period, suggests that either a longer treatment period or more frequent administration of the therapy, for example twice a day or both, might have a more marked effect. Further studies are required to examine these possibilities.

BP measurements using a mercury sphygmomanometer have the possible limitation of introducing observer bias affecting digit preference. However the antihypertensive effect of device-guided breathing has been demonstrated in various studies using different methodologies, including 24-h ambulatory BP monitoring,[18] digital BP office monitoring,[17] home BP monitoring[17,21] and office mercury sphygmomanometer measurements.[16,20] The same treatment protocol was used in all these studies. Staessen[40] compared BP changes during active antihypertensive treatment and placebo, as assessed by conventional sphygmomanometry and ambulatory BP measurement. The results show that the net treatment effect, measured by these two methods may be comparable, in spite of differences in the absolute BP changes that can be attributed to the white coat effect and limitations of measurement method. Future studies should be blinded and should consider using ambulatory BP monitoring at baseline and at the end of the study to diminish bias.

A choice was made of 'usual care' as a control instead of an active control as described in the Materials and methods section. However, it may be mentioned that earlier studies using a Walkman, under the same conditions as the intervention group,[16,17] have already demonstrated the efficacy

of slow breathing exercises using the RESPeRATE device in lowering BP. Future studies should consider using a control group doing breathing exercises at a normal rate under the same conditions as the intervention group that are doing slow breathing.

In a recent small controlled study, carried out on 30 patients with type II diabetes mellitus, Logtenberg *et al.*[23] reported no significant difference in BP changes between a group performing slow breathing and a control group that listened to music, although both groups showed significant BP reductions. One possible explanation for the study's negative findings, as suggested by Parati and Caretta[39] in an accompanying editorial, is that only 9 of the 15 patients in the intervention group (60%) were successful in lowering their breathing rates to the target of less than 10 breaths per minute. This is in contrast to earlier studies in which nearly all patients demonstrated the ability to achieve slow breathing after self-training using the original user manual, which was not available in Dutch at the time of the Logtenberg study.

In conclusion, self-treatment with device-guided breathing at home for 2 months by non-insulin-dependent diabetic patients was associated with a significant reduction in office systolic BP. The patients demonstrated good compliance with the treatment that was found to be safe. This device-guided breathing may be a low-risk, adjunctive therapy for the treatment of hypertension associated with type II diabetes mellitus.

What is known about the topic

- Hypertension is a common comorbidity in patients with diabetes mellitus and is associated with increased mortality. Many of these patients have blood pressures above the recommended level.
- Daily paced breathing exercises have been shown to reduce BP in non-diabetic hypertensive patients.

What this study adds

- Self-treatment with device-guided breathing at home for 8 weeks by non-insulin dependent diabetic patients is associated with a substantial reduction in office systolic BP.

Acknowledgements

We thank Jeremy Kark and Joseph Herman for their valuable comments.

Conflict of interest

Dr Benjamin Gavish is the Chief Scientist and Dr Ariela Alter is the Director of Clinical Regulatory Affairs at Intercure Ltd, the manufacturer of the RESPeRATE device, which supported this study.

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