Original Article

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Beneficial impact of visual stimulation-based digital therapeutics on blood pressure control in non-hypertensive individuals

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SUMMARY Hypertension-related diseases occur in both hypertensive and non-hypertensive individuals. However, few studies to date have explored blood pressure (BP) control in non-hypertensive individuals. This before-after study aimed to examine the impact of visual stimulation-based digital therapeutics (VS-DTx) on BP and heart rate (HR). Eighty-three eligible non-hypertensive participants were included in this study. The McNemar test and Paired Samples Wilcoxon Signed Rank Test were employed to assess decline rates and differences in BP and HR between the control phase and the intervention (using VS-DTx) phase. Pairwise correlation analysis was used to analyze the correlation between the two phases. This study found the systolic BP (SBP) and mean arterial pressure (MAP) in the VS-DTx phase showed a downward trend (66.2% *vs* 49.3%; 68.7% *vs* 55.4%). The mean SBP decreased from 114.73 mm Hg to 111.18 mm Hg, and the mean MAP decreased from 87.96 mm Hg to 84.88 mm Hg in the VS-DTx phase. Paired Samples Wilcoxon Test showed differences in both ΔSBP ($Z = -3.296$; $P < 0.01$) and ΔMAP ($Z = -2.386$; $P < 0.05$) (Δ is defined as the difference between baseline and post-stimulus). The pairwise correlations analysis revealed that VS-DTx affected the MAP reduction ($r = 0.33$; $P < 0.01$) between the browsing digital devices phase and the VS-DTx phase. The results indicated that VS-DTx may have a certain effect on BP, including SBP and MAP. This study preliminarily explored the possible effects of VS-DTx on BP, providing certain useful insights for future research in digital BP management.

Keywords vagal nerve stimulation, visual stimulation, digital therapeutics, blood pressure, heart rate

1. Introduction

Hypertension, as a leading cause of mortality, poses a substantial public health challenge. According to the World Health Organization, over one billion individuals are affected by systemic hypertension, leading to 7.5 million deaths worldwide annually, representing 13% of total global mortality (*1,2*). Studies have demonstrated that hypertension, the most important and modifiable risk factor for ischemic heart disease, cerebrovascular disease, as well as chronic kidney disease in humans, has emerged as a global public health concern (*3,4*). It has been suggested that better blood pressure (BP) control leads to a reduced risk of future cardiovascular events. Systolic BP (SBP) of at least 110 mm Hg has been related to multiple cardiovascular and renal outcomes. It was associated with more than 10 million deaths and 212 million disability-adjusted life-years in 2015, a 1.4-fold increase since 1990 (*4,5*). This indicates that people suffer from hypertension-related diseases regardless of high or previously considered optimal (defined as SBP of less than 120 mm Hg and diastolic BP (DBP) of less than 80 mm Hg) BP. In this regard, maintaining a relatively low BP within the normal range may aid in the prevention of potential cardiovascular disease (CVD).

Current treatments for hypertension, encompassing pharmacological and non-pharmacological interventions, are not applicable to normotensive adults seeking to prevent hypertension. Guidelines at present do not advocate for medication usage to regulate blood pressure in individuals without hypertension (*6*). While certain non-pharmacological treatments like renal sympathectomy and invasive vagal nerve stimulation (VNS) have demonstrated efficacy, they are accompanied by notable side effects (*7*). The recent introduction of transcutaneous VNS (tVNS), a non-invasive VNS therapy, poses challenges due to its intricate operation, substantial equipment prerequisites, and associated costs (*8*). Guidelines recommend certain preventive measures for hypertension, such as moderate exercise and a healthy diet. These measures have an effect on the regulation of BP levels but need to be long-lasting to realize their full potential. Consequently, an effective, non-pharmacological, and non-invasive daily method for blood pressure management is urgently required. A contemporary health management strategy labeled as "digital therapeutics (DTx)" has surfaced in recent years, leveraging digital platforms such as smartphone applications for the prevention and management of medical conditions (*9,10*). As a non-pharmacological and non-invasive BP management approach with great potential, DTx holds promise in opening a new horizon to help non-hypertensive individuals control their BP. There have been limited studies on this topic. Therefore, research is urgently needed to fill these gaps. This study presents a fresh outlook and preliminary exploration of the potential impact of DTx on BP levels.

The vagal nerve plays an essential role in maintaining physiological homeostasis. Given its innervation of the heart, VNS has been explored as a potential treatment for CVD (*11,12*). It has been confirmed to effectively improve left ventricular hemodynamics in heart failure patients, ameliorate post-myocardial infarction remodeling in the myocardium, and reduce the risk of atrial fibrillation, *etc*. (*12,13*). Studies have shown that a decrease in vagal cardiac tone is associated with and contributes to the development and maintenance of high BP (*14*). As a result, VNS has been investigated as an alternative treatment for hypertension. However, existing VNS treatment options are generally invasive, expensive, and associated with side effects (such as dysphonia, vocal hoarseness, dyspnea, paresthesia, and pain) (*8,15*). These operations are so complicated that they need medical support in the meantime–furthermore, the aforementioned treatments primarily target diagnosed hypertension and other CVDs (*16*). Indeed, there is a lack of a practical approach to assist non-hypertensive individuals in managing their BP.

Numerous studies have shown that both images and colors can influence human perception to varying extents (*17,18*). The optical images, with blurred patterns and moving plaids, are thought to induce VS and visual bistability (*19*). Visual bistability is a perceptual stimulus and is thought to potentially induce VNS (*19,20*). Building upon these theoretical foundations, we developed a smartphone application designed to stimulate the vagal nerve through the use of optical images. Through our study, we conducted a preliminary exploration of the effects of VS-DTx on BP and expect to provide a little useful guidance for the future development of non-invasive, non-pharmacological, cost-effective, and safe methods of BP control.

2. Methods

This before-after study involved participants from western and eastern China. It was conducted by the principles of the Declaration of Helsinki. All participants have read and signed the electronic form of informed consent before participating. The protocol was approved by the Ethics Committee of Chongming Hospital Affiliated to Shanghai University of Medicine and Health Sciences (CMEC-2022-KT-54).

2.1. Participant

Participants were recruited between January 2023 and February 2023. They were screened for eligibility after informed consent was obtained. A total of 95 individuals with a clinic-based SBP of 90-140 mm Hg and/or DBP of 60-90 mm Hg (from at least three separate visits) were enrolled. 83 participants, ranging in age from 18 to 65 years old (mean = 39.43; SD = 11.41), were assigned to the study, including 32 males and 51 females. The main reason for exclusion was not meeting the diagnostic criteria of normal BP. Before participating in the experiment, participants were informed about potential side effects, including possible dizziness and a decrease in BP due to VNS. Participants were required to abstain from taking antihypertensive medications or any other medications that could affect BP within the preceding two months. Individuals with any form of CVD, epilepsy, uncontrolled diabetes, severe mental illness, drug or alcohol abuse, pregnancy, and who have contraindications for the use of VNS were also excluded, as were those who had previously participated in another research trial. Additionally, Participants were instructed not to consume caffeine, smoke, or experience hyperkinesia on the day of the experiment.

2.2. Intervention

Prior to commencing the study, participants were required to rest in a quiet room for a minimum of 15 minutes. Following this, participants were asked to receive interventions, which included blank control and VS-DTx intervention. The intervention measure of the blank control was to have participants browse digital devices (view relaxing short video content) for five minutes as the browsing digital devices phase. The measure of the VS-DTx intervention was instructed to utilize the VS-DTx app for five minutes as the VS-DTx phase (see Figure 1A). Each participant underwent both blank control and VS-DTx intervention, separated by a 24-hour washout period. Due to the variations in BP at various times of the day, this would negate the impact of the control phase and ensure that both phases were carried out at the same time for two consecutive days (*21*). To achieve blinding, the order of the interventions received by participants was randomized. The study was

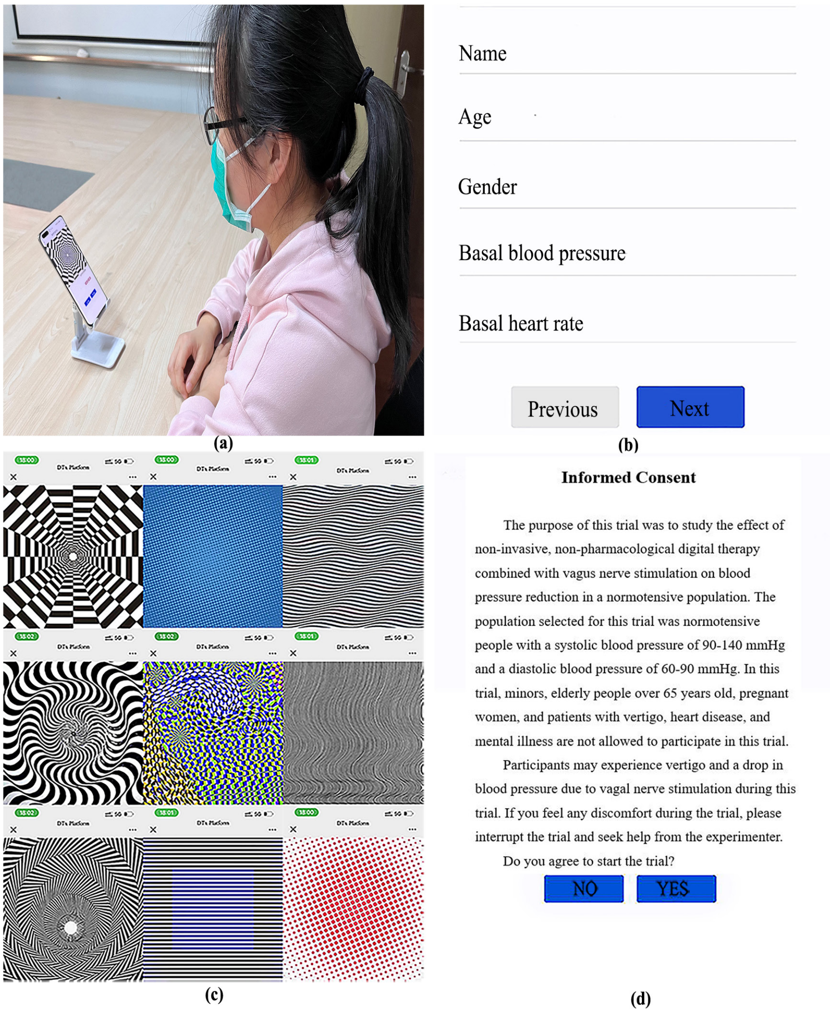

Figure 1. The main interface of this app. **(a)** Participant in VS-DTx phase. **(b)** The basic information. **(c)** The visual stimulus images. **(d)** Informed consent (English translation version).

conducted in a quiet room without any other distractions, and the digital devices running the app were positioned at a visual distance of 30 cm from each participant. This app (see Figures 1B-1D) contains basic information, informed consent, and VS images (which were selected from the optical art style).

2.3. Measures

The within-subjects approach used in this study has the advantage of effectively controlling the influence of subjects' variables on the results (*22*). The study included two phases: the browsing digital devices phase and the VS-DTx phase. The dependent variables are BPs, HR, ΔBPs, and ΔHR. BPs include SBP, DBP, and MAP. SBP and DBP are defined as the amplitude of the peak and the trough of the BP waveform, respectively. MAP represents the average BP within a single cardiac cycle (MAP = 1/3 SBP + 2/3 DBP), and HR is defined as the number of heartbeats in a minute (*23*). The process of measuring BP was performed according to a standard protocol recommended by the 2018 Chinese Guidelines for Prevention and Treatment of Hypertension (*24*). An assessor measured participants' BP and HR using a standard arm BP cuff and a sphygmomanometer in the brachial artery. The measurement was performed on each arm of the participants to obtain two sets of HR and BP values (two DBP values and two SBP values). The average of the two HR values, the two DBP values, and the two SBP values were calculated separately as the final HR, DBP, and SBP values, and the final MAP was calculated with the final SBP and final DBP. The automatic mode of the sphygmomanometer was used to measure BP without the need for intervention by the assessors other than to place the cuff and switch the device on.

2.4. Experimental procedure

According to previous studies, BP exhibits diurnal variations, with higher readings observed in the morning (*25*). To mitigate the potential impact of different times of day on the experimental outcomes, all subjects were measured within the predetermined period. The standard

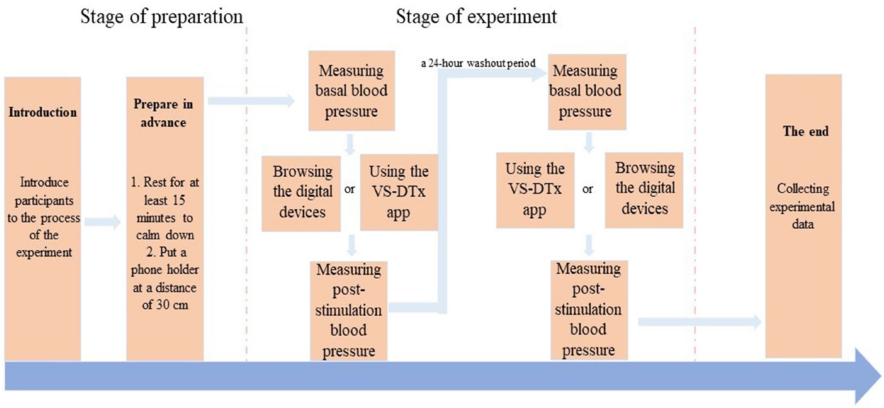

Figure 2. Standard experimental procedure.

Table 2. Descriptive statistics physiological indexes for the different phases

Phase	Baseline browsing digital devices M (S.D)	post-stimulus browsing digital devices M (S.D)	Baseline VS-DTx M (S.D)	post-stimulus VS-DTx M (S.D)
SBP	113.90 (11.45)	113.77 (11.12)	114.73 (11.15)	111.18 (10.83)
DBP	75.43 (7.32)	73.89 (7.81)	74.57 (7.88)	71.73 (8.39)
MAP	88.26 (8.19)	87.18 (8.42)	87.96 (8.42)	84.88 (8.50)
HR	75.84 (9.34)	74.90 (9.07)	75.34 (9.11)	74.34 (9.75)

Table 1. Baseline characteristics of the participants

AGE (YEARS)	39.45 ± 11.39
MALE, N (%)	32 (38.6)
BMI (KG/M^2)	23.26 ± 3.65

experimental procedure is illustrated in Figure 2. On the first step of the experiment, participants received a comprehensive introduction to the experimental environment and procedure. Subsequently, they were instructed to sit quietly for a minimum of 15 minutes to allow any BP changes induced by tension to dissipate. BP and HR measurements were then taken to establish baseline values. After that, the participants sat in a chair, positioned at a visual distance of 30 cm in front of them. They were randomized to decide whether to receive the blank control or the VNS-DTx intervention first. After 5 minutes, post-stimulus BP and HR measurements were obtained. Following a 24-hour interval, a similar procedure was repeated. Participants were asked to perform another intervention that they had not previously received (using the VS-DTx app or browsing digital devices). Baseline and post-stimulation BP and HR measurements were recorded as well.

2.5. Statistical analysis

The analysis was performed using STATA statistical software (version 15.0, StataCorp, Texas, USA), with a *P*-value of < 0.05 indicating statistical significance. Data normality was assessed with the Shapiro-Wilk normality test. Continuous variables conforming to a normal distribution were compared using a Paired-Samples *T*-Test, whereas those that were not normally distributed were tested using the Paired Samples Wilcoxon Signed Rank Test. Differences in proportions were compared by using the McNemar test. Furthermore, pairwise correlations analysis was used to investigate the correlation between browsing digital devices and VS-DTx phases.

3. Results

The baseline characteristics are shown in Table 1 and the descriptive statistics for the physiological indexes for the different phases collected are shown in Table 2.

There were two phases in this study, including the browsing digital devices phase and the VS-DTx phase. McNemar test showed that the proportions of decrease in SBP, DBP, MAP, and HR in the VS-DTx phase were 66.2%, 61.4%, 68.7%, and 61.4%, respectively, whereas the proportions during the browsing digital devices phase were 49.3%, 55.4%, 55.4%, and 50.6%. And there were significant differences between the two phases for the ratio of SBP reduction ($\chi^2 = 4.45$; $P < 0.05$), and MAP reduction ($\chi^2 = 3.90$; $P < 0.05$), but it did not show any significant differences for DBP ($\chi^2 = 0.76$; $P > 0.05$) and HR ($\chi^2 = 1.88$; $P > 0.05$). Further paired comparisons were needed due to the finding of this study that there were overall significant differences in SBP and MAP, at least.

To investigate the differences in BP and HR reduction between the browsing digital devices phase and the VS-DTx phase, a set of Paired Samples Wilcoxon Test was performed. Significant differences were found on both ΔSBP (Z = - 3.296; $P < 0.01$) and ΔMAP (Z = - 2.386; $P < 0.05$). The data further showed that the BP reductions after VS were greater than those from browsing digital devices. Moreover, a Paired Samples Wilcoxon test was performed to investigate ΔDBP and ΔHR. Results showed that there were no significant differences between the two phases on both ΔDBP ($P > 0.05$) and ΔHR ($P > 0.05$). Higher reductions of DBP and HR after VS were observed than those in the browsing digital devices phase. However, the differences were not significant. All these results are shown in Figure 3.

Furthermore, the scatter plot showed the linear correlation and the stability of the difference between the two phases (see Figure 4). According to the result of pairwise correlations, it is evident that the stability of the difference in MAP ($r = 0.33$; $P < 0.01$) is significant, indicating a high possibility for VS-DTx to have an impact on overall BP control.

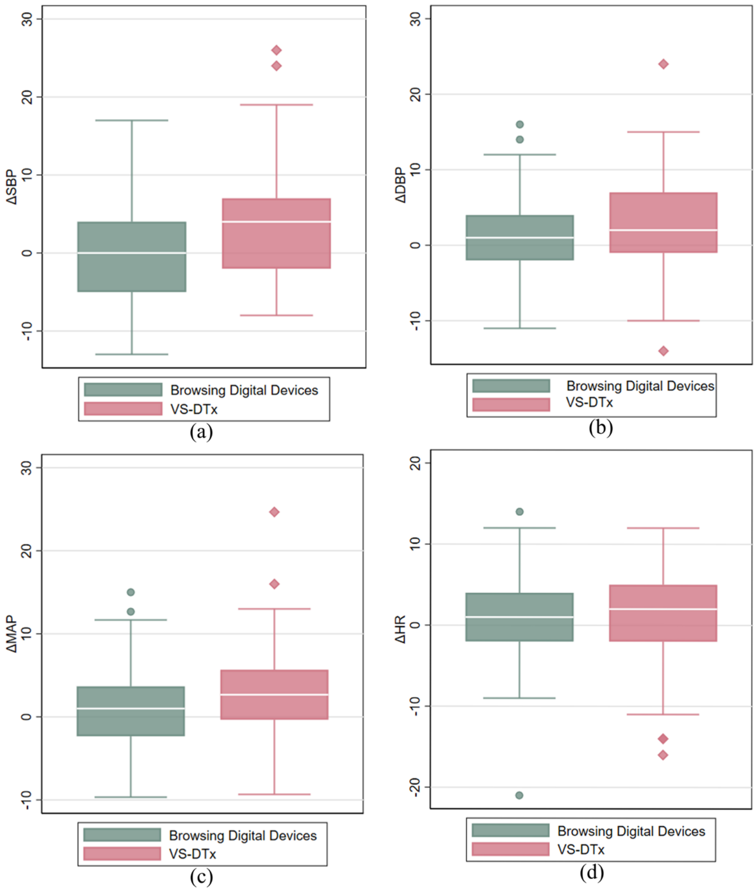

Figure 3. The results of Paired Samples Wilcoxon Test on ΔSBP, ΔDBP, ΔMAP, ΔHR in different phases, and the results of the distribution of the median are shown in the figure. (a) ΔSBP in browsing digital devices phase and VS-DTx phase (Z= -3.296; $**P < 0.01$), very significant difference. **(b)** ΔDBP in browsing digital devices phase and VS-DTx phase ($P > 0.05$), no significant difference. **(c)** ΔMAP in browsing digital devices phase and VS-DTx phase (Z= -2.386; $*P < 0.05$), significant difference. **(d)** ΔHR in browsing digital devices phase and VS-DTx phase ($P > 0.05$), no significant difference.

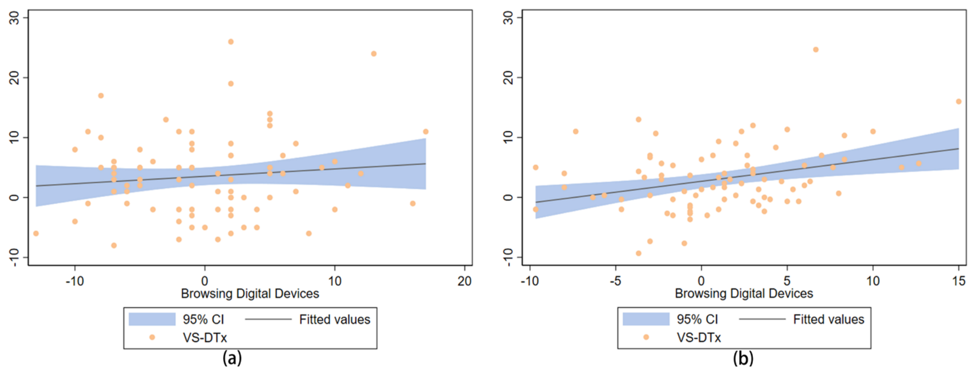

Figure 4. Scatterplot depicting the correlation between browsing digital devices phase and VS-DTx phase. (a) Scatterplot of ΔSBP. **(b)** Scatterplot of ΔMAP ($r = 0.33$; $**P < 0.01$), very significant difference.

4. Discussion

VNS has exhibited remarkable efficacy in controlling BP in multiple studies. Early research in dogs in 1960 showed that VNS induced bradycardia and reduced atrial contractility, resulting in decreased ventricular filling and stroke volume, ultimately leading to BP reduction (*26*). Recent research has demonstrated that long-term activation of vagal parasympathetic pathways can restore autonomic balance and potentially serve, which is an effective treatment for hypertension in an animal model of neurogenic hypertension (*27*). In human subjects, VNS research has mainly focused on treating epilepsy since the late 1990s. As limited data from human trials is available, research on treating hypertension has only recently begun to grow (*28*). Early VNS devices necessitated the placement of bipolar electrodes encircling the cervical vagal nerve and the subcutaneous implantation of a generator in the chest wall. The surgical technique has been associated with a large number of surgical complications and side effects, including wound infection, cardiac arrhythmia under test stimulation, electrode malfunction, hoarseness, dysphagia, cough, and pain (*29*). Recently, tVNS has been used for BP control. It is a noninvasive device composed of electrodes placed on the skin of the external ear, and connected to a stimulating box (*30*). While tVNS effectively regulates BP, it does require complex parameter settings, specialized treatment equipment, and professional guidance (*8*). Neither the VNS techniques nor the pharmacological therapies detailed above are suitable for daily BP regulation in normotensive individuals. This study explored a novel non-invasive and non-pharmacological DTx approach, and we demonstrated that DTx had certain effects on BP. Its strength lies in its high acceptance, mild side effects, ease of use, and short treatment course. If it can be put into use in the future, users will be more inclined to adhere to it.

It is widely recognized that BP and HR are closely interrelated. As the heart pumps more blood per minute, it increases the lateral pressure on the vascular wall, leading to an elevation in BP. Conversely, when the HR slows down, the lateral pressure on the vascular wall from the blood flow decreases, resulting in a drop in BP. Simultaneously, changes in HR can be secondary to fluctuations in BP. A dip in BP triggers a response from the heart, causing it to be affected by negative feedback, leading to an increase in HR (*31,32*). In the present study, it was observed that HR did not exhibit a significant change in the VS-DTx phase compared to the browsing digital devices phase, while certain changes in BP value were noted. This finding suggested that the effect of VS-DTx on BP was independent of alterations in HR. Instead, it may directly impact SBP and MAP to affect BP.

In the present study, there was no significant change in DBP before and after the intervention. This could be attributed, in part, to the fact that DBP values are generally smaller compared to SBP (approximately 2/3 of SBP) and have a narrower range of variation after stimulation. Meanwhile, the intensity of VS on the vagal nerve is not as strong as direct stimulation (*e.g.*, invasive VNS and tVNS). Therefore, weak vagal nerve stimulation may not lead to a significant variation in DBP. Furthermore, the participants in this study used the app for only five minutes, which may also contribute to the lack of significant change. Chinese hypertension treatment guidelines place greater emphasis on SBP due to stronger evidence of its association with CVD endpoints (*33*). Also, MAP is an important indicator of the average BP level, as it is linearly correlated with all types of CVD endpoints (*34*). In the present study, VS-DTx primarily affected on SBP and MAP, indicating that the impact of VS-DTx on overall BP should not be disregarded, despite the insignificant change in DBP.

Numerous studies have consistently shown that maintaining BP at low levels (within normal ranges) is beneficial to health. One recent investigation found that each 5 mm Hg reduction in SBP was associated with a 10% relative risk reduction of major cardiovascular outcomes, including a 13% less risk for stroke, 7% for ischemic heart disease, 14% for heart failure, and 5% for death (*35*). A prospective study confirmed that people in the higher fitness category had lower BP than those in the lower fitness category (*36*). A recent study examined the effects of standard BP control and intensive BP control in the hypertensive population. Researchers found that lowering SBP to less than 120 mmHg (the intensive goal) resulted in a significant reduction in fatal and nonfatal cardiovascular events, as well as mortality from any cause, compared to the standard goal of less than 140 mm Hg (*37,38*). American College of Cardiology/American Heart Association (ACC/AHA) released guidelines for the management of hypertension in adults in 2017, defined hypertension as an SBP > 130 or a DBP > 80 mm Hg, and defined an SBP of 120-129 or a DBP of 70-79 mm Hg as elevated BP (*39*). The latest 2022 Chinese Clinical Practice Guidelines for Hypertension recommend lowering the diagnostic threshold for hypertension in Chinese adults from SBP ≥ 140 mm Hg and/or DBP ≥ 90 mm Hg to SBP ≥ 130 mm Hg and/or DBP ≥ 80 mm Hg (*6*). Although the benefits of intensive BP control are widely recognized, attention should also be given to BP control in non-hypertensive adults. In this present study, it was found that the mean SBP decreased from 113.77 mm Hg to 111.18 mm Hg, while the mean MAP decreased from 87.18 mm Hg to 84.88 mm Hg. The results also showed significant differences in both ΔSBP ($Z = -3.296$; $p < 0.01$) and ΔMAP ($Z = -2.386$; $p < 0.05$), indicating that VS-DTx had a certain impact on SBP and MAP. These findings suggest that non-hypertensive patients may benefit from VS-DTx.

With the advent of the digital age, there has been an increasing addiction to mobile electronic devices. This shift highlights the need for a modern approach to health management. Clinical guidelines have provided recommendations to help non-hypertensive adults control their BP, such as maintaining a balanced diet, engaging in moderate exercise, controlling weight, and quitting smoking and alcohol consumption, as well as practicing meditation and yoga. While these methods are practical and effective, they can be slow to take effect, making adherence difficult. VS-DTx, a digital approach to health management, is ideally suited to be embedded in hand-held devices like cell phones and electronic watches. This advanced approach enables people to conveniently control their BP anytime and anywhere, especially younger populations who may have lower awareness and treatment rates for hypertension but are highly skilled in using electronic devices. The accessibility and convenience offered by this digital method empower individuals to take charge of their BP management in a more user-friendly manner. This study aimed to conduct a preliminary exploration investigation into the possibility of the impact of VS-DTx on BP, explore the potential of using VS-DTx to assist in controlling BP in non-hypertensive adults, and provide some new insights for future health management.

5. Limitations

Some limitations should be considered in the present study. First, the sample size was relatively small. Studies with larger sample sizes may be necessary to observe more striking differences. Second, the sampling was limited to two regions in China, which may restrict the generalizability of the results to the broader population. Moreover, the gender ratio in this study was not evenly balanced, with 32 males and 51 females, and this imbalance may potentially influence the findings. Furthermore, the study only focused on youth and middle-aged individuals. The sensitivity of BP and HR to VS may vary across different populations, and it is important to investigate the effects in diverse groups. Future trials should aim to include a wider range of individuals to enhance the generalizability and applicability of the findings. Additionally, this study was primarily intended to conduct a preliminary exploration of the effects of VS-DTx on BP. The study results can only indicate certain changes in some BP values and do not clarify the therapeutic effect of the method. In the future, building upon this study, more mature products can be developed to facilitate more comprehensive research for validation.

6. Conclusion

VS-DTx may have an impact on BP management, providing some useful insights for future research in digital BP management.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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