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BRIEF COMMUNICATION

Low-intensity walking as mild medication for pressure control in prehypertensive and hypertensive subjects: how far shall we wander?

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Successful prevention and treatment of hypertension depend on the appropriate combination of antihypertensive drug therapy and nondrug lifestyle modification. While most hypertension guidelines recommend moderate- to high-intensity exercise, we decided to explore a mild yet effective type of exercise to add to hypertension management, especially in populations with complications or frailty. After comparing the short-term cardiovascular effects of low-speed walking versus high-speed walking for 3 kilometers (km) (3 km/h versus 6 km/h) in young, healthy volunteers, we delivered low-speed walking (low-intensity walking, 2.5 metabolic equivalents of task, METs) as exercise therapy in 42 prehypertensive and 43 hypertensive subjects. We found that one session of 3 km low-intensity walking exerted a transient pressure-lowering effect as well as a mild negative chronotropic effect on heart rate in both the prehypertensive and hypertensive subjects; these short-term benefits on blood pressure and heart rate were accompanied by a brief increase in urine β-endorphin output. Then we prescribed regular low-intensity walking with a target exercise dose (exercise volume) of 500–1000 METs·min/week (50–60 min/day and 5–7 times/week) in hypertensive subjects in addition to their daily activities. Regular low-intensity walking also showed mild but significant blood pressure-lowering and heart rate-reducing effects in 7 hypertensive subjects within two months. It is hypothesized that regular low-intensity exercise of the necessary dose could be taken as a pragmatic and supplementary medication for hypertension management.

Keywords: hypertension; prehypertension; exercise medication; low-intensity walking; metabolic equivalent of task; blood pressure; heart rate; urine β-endorphin

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INTRODUCTION

Physical activity, intentionally or not, is a ubiquitous physiological phenomenon throughout the human lifespan. It is also a pivotal process of adaptation to the ever-changing environment. However, as our society develops, physical activities are increasingly being replaced by automobiles and other machines, and a sedentary lifestyle prevails. Physical inactivity and excessive sitting are considered to be among the major risk factors for cardiovascular disease, including hypertension, the single most important factor contributing to cardiovascular events. It has also been found that people who regularly engage in moderate or vigorous exercise have low rates of cardiovascular events and all-cause mortality. Therefore, public health guidelines recommend regular exercise for adults, usually calling for moderate- to high-intensity aerobic exercise for a cumulative total of at least ≥150 min/week or vigorous exercise for ≥75 min/week [1]. Accordingly, hypertension guidelines recommend prescribing ≥30 min/day of continuous or cumulative moderate dynamic exercise 3–7 days/week for hypertensive patients in addition to the routine activities of daily living [2–4].

Moderate- to high-intensity exercise and endurance training are popular among healthy people for competition and recreational purposes. However, when such regimens are chosen as medication in the management of hypertension, middle-aged or older adults performing moderate or vigorous exercise sometimes encounter maladaptation problems, such as exercise-induced joint pain, prolonged palpitation/arrhythmia, chest tightness or dyspnea, and even ischemic episodes that prevent them from exercising further [5]. Most of the problems are due to exercise-related overload of the cardiovascular system with relative hypoperfusion of the organs involved during vigorous exercise, since a large portion of the blood would be allocated to the active skeletal muscles.

These problems raise a number of questions to be answered: Does vigorous exercise truly help reduce cardiovascular events in hypertension? Do we have effective yet safe exercise prescriptions for hypertension at the population level? Should we strive to explore exercise approaches with fewer unwanted reactions for hypertensive patients, just as we struggle to develop antihypertensive drugs with fewer adverse effects?

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It is generally supposed that low-intensity exercise is of little value for lowering blood pressure. However, there is little scientific evidence to confirm or refute this suggestion. We are intrigued to observe the potential benefits of mild exercise for blood pressure control; to explore a safe and feasible substitute for moderate- or high-intensity exercise in middle-aged or older subjects for hypertension management, providing the sedentary hypertensive individuals with complications a convenient way to begin with; and to look for a well-tolerated exercise mode that could be implemented in frail subjects with chronic illness in their daily life over a relatively long period.

Does low-intensity exercise lower blood pressure?

In a pioneering study [6], we compared the short-term cardiovascular effects of 3 kilometers (km) of low-speed walking (3 km/h, 2.5 metabolic equivalents, METs) versus high-speed walking (6 km/h, 4.5 METs) in young volunteers aged 18–27 years, aiming to observe the effects of low-intensity exercise (< 3 METs) on blood pressure (BP). Low-speed walking (low-intensity walking) but not high-speed walking (moderate-intensity walking) reduced BP within 10 min after the walk. In addition to reducing BP, low-intensity walking transiently decreased the resting heart rate (HR). The reduction of BP and HR in young volunteers were accompanied by increased urine β-endorphin output during low-intensity walking [6].

One session of low-intensity walking, specifically, 3 km/h for one hour, also briefly but significantly reduced the resting BP of stable hypertensive subjects (BP < 160/100 mmHg hypertensive subjects with or without antihypertensive drugs), and the resting HR was also decreased significantly after walking [6]. There was no significant fluctuation of BP during low-intensity walking. These results are consistent with the findings of our previous animal study, in which low-intensity treadmill running (30% of maximal aerobic velocity) reduced BP in spontaneously hypertensive rats [7].

Benefits of 3 km of low-intensity walking in prehypertensive subjects

Here, we reported the effects of one low-intensity 3-km walk on short-term BP and HR in prehypertensive subjects. Forty-two volunteers with high normal BP (prehypertensive, systolic BP 120–139 mmHg and/or diastolic BP 80–89 mmHg) and fifty-two age-matched control subjects with optimal BP (optimal normotensive control, systolic BP < 120 mmHg and diastolic BP < 80 mmHg) were recruited. The blood pressure criteria were in accordance with the Chinese Guideline for Hypertension Prevention and Management published in 2015, and resting BP and HR prior to the commencement of the walking study were measured at the upper arm with an electronic sphygmomanometer (OMRON HEM-7136) using the standard method recommended by the guideline [4]. The study was approved by the Human Ethics Committee of Shanghai Jiao Tong University School of Medicine, and written informed consent was obtained from the participants.

The participants followed a trained researcher who walked at a slow pace of up to 3 km/h (approximately 2.5 METs according to the Compendium of Physical Activities published in Medicine & Science in Sports & Exercise) [8]. Each session of low-intensity walking sustained for 50–60 min. All the walking sessions were implemented by trained researchers who accompanied the participants in groups of two to five or individually to control walking speed and performed measurements and recordings. The subjects' BP and HR were measured in the sitting position before walking (prewalk baseline), immediately, 5 min, and 10 min after walking (postwalk) with an electronic sphygmomanometer (OMRON HEM-6111) with the wrist at the level of the heart. Cardiac workload was represented as systolic BP timed by HR (systolic BP × HR). When performing a walking study, we chose to measure BP and HR at the wrist for quick recording of instant values at different points, saving time of handling clothes and adapting frequent position adjustments. Therefore, all the data presented for comparison were values measured in the same way at the same wrist with one person using the same sphygmomanometer. This method made the readings of different measurements comparable.

The walking was usually performed in the open air during workday breaks or weekends at the convenience of the research subjects, adjusted to the subjects' daily lives. When it was too hot or too cold outside, the walking was carried out down indoor corridors or halls to prevent the influence of dramatic temperature fluctuation on BP and HR. No music or energetic speaking was allowed during walking.

After a low-intensity 3-km walk, resting BP and HR both decreased significantly within 10 min in optimal normotensive controls and prehypertensive subjects (Table 1). It was also found that in addition to higher baseline BP, subjects in the prehypertensive group showed significantly higher baseline values of resting HR and thus increased cardiac workload compared with that of optimal normotensive controls (Table 1).

A subgroup of participants had high resting HR (frequently exceeding 90 beats/min on physical check-ups and/or electrocardiogram recording), excluding fever, hyperthyroidism, myocarditis, and chronic heart failure. The resting HR of the subgroup ($n = 13$) was 97 ± 7 beats/min, ranging from 88 to 117 beats/min before walking. The low-intensity walking rendered marked HR reduction in these research subjects (5-min and 10-min postwalk values were 86 ± 9 beats/min and 87 ± 8 beats/min, respectively, $P < 0.01$ versus prewalk values). The mean values of HR reduction were -11 ± 7 and -10 ± 6 beats/min at 5 and 10 min after walking. Among these participants, coffee and/or tea usage was common, and two of them had been diagnosed with severe anxiety at general hospitals.

Effects of low-intensity walking on hypertension: single session versus regular sessions

Based on previous findings, we further studied the effects of a single session of 3-km low-intensity (<3 METs, low-MET) walking and regular low-intensity walking (repeated low-MET walking for 2 months) on BP and HR in hypertensive subjects. The study was approved by the Human Ethics Committee of Shanghai Jiao Tong University School of Medicine, and written informed consent was obtained from the research subjects.

Single session of 3-km low-intensity walking

The effects of a single 3-km session of low-intensity walking on short-term BP and HR were studied in forty-three hypertensive subjects (systolic BP ≥ 140 and/or diastolic BP ≥ 90, according to Chinese hypertension guidelines [4], aged 46 ± 18 years) and twenty-six age-matched normotensive controls (systolic BP < 140 and/or diastolic BP < 90, aged 45 ± 10 years).

The research subjects carried out a single session of low-MET walking with BP and HR measured in the sitting position as previously mentioned. The walking interventions were performed individually during workdays or weekends at the convenience of the research subjects. In this arm of study, research subjects' orthostatic BP was also measured every 1000 meters during walking, i.e., BP and HR were measured in upright position at the point of immediately before walking and then at 1000, 2000, and 3000 meters during walking. One-hour urine samples before walking and one hour after the beginning of walking were collected for β-endorphin and growth hormone determination (enzyme-linked immunosorbent assay kit, Wuhan Elabscience Biotechnology Co., Ltd, China), and albumin determination was performed with an immunochromatography assay kit (Shanghai Chemtron Biotech Co., Ltd, China). Coffee and tea were avoided on the day of study, and nothing was paid to the volunteers in consideration of avoiding potential psychological interference by

material incentives that might have some influence on the variables such as β-endorphin to be tested.

Similar to the results in prehypertensive subjects (Table 1), a single session of low-intensity walking acutely reduced BP, HR, and cardiac workload in hypertensive subjects as well (Fig. 1a–d). Compared with the values before walking, there were no significant changes in the mean values of orthostatic BP and cardiac workload during low-intensity walking (Fig. 1e, f). However, individual variation did exist, and three of the research subjects who used cell phones frequently during walking showed increased BP and HR either during or after walking.

Low-intensity walking also increased urine β-endorphin output briefly in both normotensive and hypertensive subjects. The urine β-endorphin output before and after walking was 12.6 ± 10.0 ng/h and 17.7 ± 14.4 ng/h in normotensive controls and 18.8 ± 13.3 ng/h and 28.5 ± 20.6 ng/h in hypertensive subjects (n = 21-24, all $P < 0.05$ compared with respective values before walking). The urine growth hormone levels before and after walking were 2.0 ± 2.0 ng/h and 2.4 ± 2.7 ng/h in normotensive controls, 4.0 ± 3.9 ng/h and 4.7 ± 3.3 ng/h in hypertensive subjects, respectively. The urine albumin values before and after walking were 0.4 ± 0.3 mg/h and 0.6 ± 0.7 mg/h in normotensive controls, 1.9 ± 3.4 mg/h and 2.7 ± 5.8 mg/h in hypertensive subjects, respectively (the albumin values were also log-transformed to normalize distribution before statistical analysis: 2.60 ± 0.31 and 2.65 ± 0.31 in normotensive controls, 2.89 ± 0.58 and 3.01 ± 0.58 in hypertensive group) (n = 18-24, all $P > 0.05$ compared with respective values before walking for both growth hormone and albumin). The higher levels of β-endorphin, growth hormone and urine albumin in the hypertensive subjects were similar to those found before and the mechanisms were discussed elsewhere [6].

Regular sessions of low-intensity walking (Redorphin Walking Heart Action)

The Redorphin Walking Heart Action (Redorphin, word coined to indicate "regular" combined with "endorphin", re + dorphin) is ongoing now and has not been completed; and we reported the protocols here, along with the partial results of a limited sample of subjects completing regular walking for two months.

The volunteers for Redorphin Walking Heart Action were enlisted from the research subjects who had previously participated in a single session of walking. All subjects were given their cardiovascular information on the spot before and after walking at their first walking session, informed of the possible benefits of regular walking, and then offered the opportunity to participate in the regular walking study. Research subjects who agreed to

Table 1. Effects of one 3-kilometer low-intensity walk on blood pressure and heart rate in prehypertensive individuals

	Optimal normotensive control	Prehypertensive	ΔOptimal normotensive control	ΔPrehypertensive
n	52	42		
Age, year	27 ± 12	28 ± 13		
Systolic BP, mmHg				
Prewalk baseline	110 ± 6	123 ± 6$^{\#\#}$		
Postwalk 0 min	109 ± 8	120 ± 10*	0 ± 6	−3 ± 8
5 min	106 ± 7**	116 ± 11**	−3 ± 5	−7 ± 10
10 min	106 ± 7**	115 ± 10**	−3 ± 6	−8 ± 9
Diastolic BP, mmHg				
Prewalk baseline	70 ± 6	81 ± 5$^{\#\#}$		
Postwalk 0 min	69 ± 6	77 ± 8**	−1 ± 6	−4 ± 7
5 min	67 ± 6**	75 ± 10**	−3 ± 5	−7 ± 9
10 min	67 ± 8**	75 ± 9**	−3 ± 5	−7 ± 9
Mean arterial pressure, mmHg				
Prewalk baseline	83 ± 5	95 ± 4$^{\#\#}$		
Postwalk 0 min	82 ± 6	91 ± 8**	−1 ± 5	−4 ± 6
5 min	80 ± 6**	88 ± 10**	−3 ± 4	−7 ± 9
10 min	80 ± 7**	88 ± 9**	−3 ± 5	−7 ± 8
Heart Rate, beats/min				
Prewalk baseline	77 ± 11	81 ± 13$^{\#}$		
Postwalk 0 min	74 ± 11**	80 ± 10	−3 ± 5	−1 ± 7
5 min	73 ± 10**	77 ± 10**	−4 ± 5	−5 ± 8
10 min	72 ± 10**	77 ± 10**	−5 ± 5	−4 ± 7
SBP × HR, mmHg·beats/min				
Prewalk baseline	8413 ± 1335	9986 ± 1547$^{\#\#}$		
Postwalk 0 min	8106 ± 1372**	9582 ± 1408**	−307 ± 745	−404 ± 831
5 min	7730 ± 1221**	8872 ± 1444**	−686 ± 632	−1114 ± 986
10 min	7631 ± 1169**	8825 ± 1386**	−780 ± 694	−1161 ± 972

Values are the mean ± SD
BP blood pressure, *HR* heart rate
*$P < 0.05$
**$P < 0.01$ versus respective prewalk baseline values
#$P < 0.05$
##$P < 0.01$ versus optimal normotensive control
Δ Changes listed for reference without statistical analysis

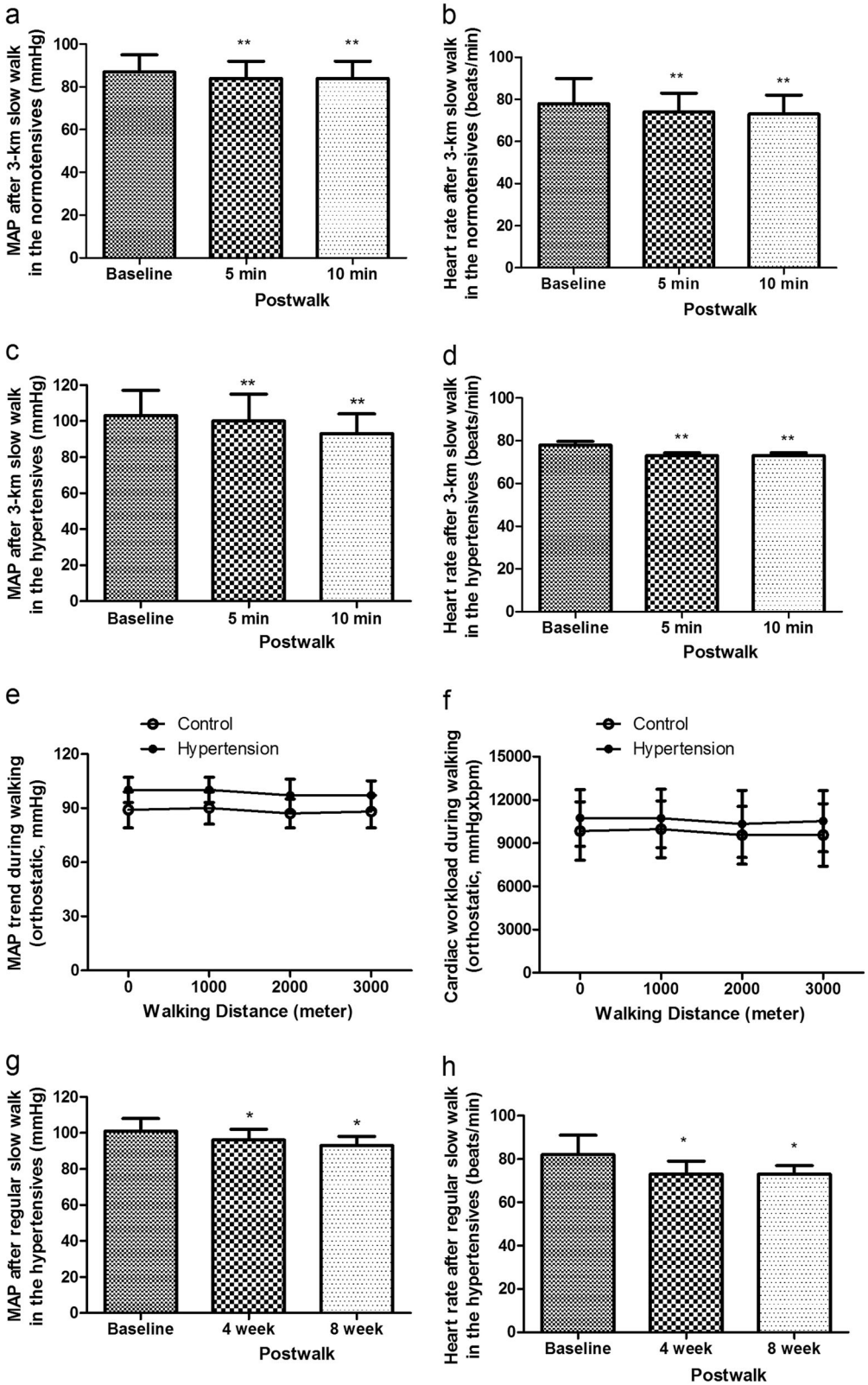

Fig. 1 Effects of low-intensity walking on blood pressure and heart rate in hypertensive subjects. From **a**–**d**, single session of low-intensity walking (slow walking) on mean arterial pressure (MAP) and heart rate (HR) in age-matched normotensive controls (**a**, **b**, $n = 26$) and hypertensive subjects (**c**, **d**, $n = 43$); **e**, **f** MAP and cardiac workload (systolic blood pressure × HR) during low-intensity walking ($n = 47$, including 24 normotensive and 23 hypertensive subjects); **g**, **h** MAP and HR in hypertensive subjects completing 2 months of regular walking ($n = 7$). Values are the mean ± SD. $^{*}P < 0.05$, $^{**}P < 0.01$ versus respective baseline values

participate in regular walking for at least 2 months were recruited. That is, at the time of enrollment, the participants completing one session of 3-km walking without difficulties were trained individually to perform subsequent regular low-intensity walking at home. All of the research subjects were tutored and supervised for methods and adherence by experienced researchers at the beginning and at regular visits face to face and communicated through phone calls any time if needed.

The research subjects of regular walking study were divided into three subgroups: the prehypertensive group (systolic BP 120–139 mmHg and/or systolic BP 80–89 mmHg), the hypertensive group (systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg) [4], and the group of subjects with high resting heart rate (resting HR frequently exceeded 90 beats/min on routine physical check-ups and/or a confirmatory electrocardiogram, excluding fever, chronic heart failure, myocarditis or hyperthyroidism). The inclusion criteria were as follows: being able to complete the single session of low-intensity walking without difficulties, community-dwelling, reporting no pending career changes, and being able to take notes and to report any unwanted events. We excluded people with acute, terminal or unstable medical conditions that would make participation in the exercise study unsafe. People who had significant alterations in living condition during walking intervention or who adjusted antihypertensive drugs on their own were also excluded (e.g., those who went abroad for a period of time or stopped taking antihypertensives abruptly when BP was under control). Age-matched subjects who did not perform regular exercise were also recruited as sedentary controls from the research subjects who participated in the single session of walking.

In the home-based and investigator-supervised regular walking study, we prescribed participants with a target exercise dose (exercise volume) of 500–1000 METs·min/week, i.e., low-intensity walking for 50–60 min/day and 5–7 times/week. This exercise dose was considered to be theoretically sufficient based on our preliminary evidence from hypertensive volunteers who had slow walking during their relatively stable daily living. For those who were frail but not with acute untreated illness, 200–250 METs·min/week was suggested to begin with, i.e., doing one or two 30-min sessions of low-MET walking per day. In all, participants were encouraged to walk 50–60 min each time per day but could also take a 30-min walk once or twice daily, tailored according to their fitness, health status, ease of walking and preference for venue. People who used to walk fast were cautioned not to resume fast walking or other moderate-intensity exercise during the regular walking study.

All participants were asked to report whether they experienced any adverse or unexpected events during or after walking. There was no requirement of adjusting antihypertensives or any other medication. After commencement of regular walking, resting BP and HR were measured every two weeks in the first month and at the end of the second month. The measurements were performed twice in the morning or afternoon during check-up visits. Participants were also trained to measure BP and HR by themselves during their daily life when needed.

Seven out of eleven hypertensive subjects enrolled thus far had completed 2-month regular walking (male 5, female 2, aged 53 ± 17 years), and two of them were on antihypertensives. The body weight was 25.6 ± 4.6 kg/m^2 at the beginning and 24.5 ± 3.9 kg/m^2 after 2 months of regular walking ($P > 0.05$). After commencing regular walking, two subjects who reported heel pains and one who reported tiredness during a 60-min walk changed to two 30-min walks daily within the first week of the study. After the adjustments, the above symptoms disappeared, and they increased the exercise dose gradually thereafter. Three participants withdrew from the study within two weeks due to limited time and one withdrew because of doing moderate-intensity exercise outside our study prescription. Three participants reported relaxation and obvious sleepiness after a slow walk. No short of breath or palpitation or other adverse events were reported by the participants during the study.

After low-intensity walking, hypertensive subjects had mild but significant lowering of BP and HR (Fig 1g, h) without adding or adjusting antihypertensive drugs. The significantly decreased HR after repeated low-intensity walking, which indicated decreased sympathetic nervous activity, would have played a role in the BP reduction.

It is worth mentioning that there was one 65-year-old who had been diagnosed with hypertension and severe anxiety for half a year but declined to take antihypertensive or anxiolytic drugs. He also had long-standing insomnia and type 2 diabetes. This participant saw the readings of obvious HR reduction just after his first slow walk (resting HR reduced from 89 beats/min to 83 beats/min) and decided to join the regular walking study immediately. The ELISA testing of his urine revealed marked elevation of β-endorphin output after a 3-km slow walk (urine β-endorphin from 14.0 ng/h before walking elevated to 33.8 ng/h). He kept slow walk once or twice daily for up to at least 60 min per day. On the tenth day, he himself reported marked BP and HR reduction as well as better glucose control and significant sleeping improvement. He had been free of any tranquilizing medication when completing 2-month regular walking. Previously on two types of hypoglycemics, he was now on a single pill (metformin only), and he had been keeping the habit of slow walking ever since (for over eight months by now). This finding is consistent with our animal study that long-term mild exercise increased insulin sensitivity in spontaneously hypertensive rats in addition to cardiovascular benefit [7]. Such a single case study was of potential value because it could reveal important facts leading to new clues and further investigations in various fields.

Although the sample size was too small to arrive at final conclusion, the beneficial effects of regular low-intensity walking observed up to now are obviously encouraging, and further volunteer enrollment for Redorphin Walking Heart Action is being carried out.

Working (walking) hypothesis of low-intensity exercise as medication

As the idea of “Exercise is medicine” becomes popular, we hypothesized that exercise should be prescribed individually depending on exercise type, intensity, indication and potential adverse reactions for special subjects, just like prescribing any antihypertensive drugs, especially when considering “high-dose” exercise for hypertensive individuals.

To date, most studies on exercise physiology have been carried out in athletes participating in sports and recreational endurance training, where high-intensity physical activity and overtraining have long been recognized as a complex physical stress accompanied by marked activation of the sympathetic system and the hypothalamus-pituitary-adrenal axis. Elevated oxidative stress, inflammation, skeletal muscle damage, maladaptation or even mood disturbance (the overtraining syndrome) occurred in some athletes [9–11]. Enormous blood vessel beds dilate during vigorous exercise, and cardiac output elevates significantly (mainly by increasing heart rate, Fig. 2) to meet the soaring need of skeletal muscle metabolism. Profuse sweating helps prevent body overheating to a lethal degree, but a large amount of body fluid loss could also lead to hypovolemia during exercise. In addition to massive epinephrine and norepinephrine release, adrenocorticotropic hormone and cortisol increase accordingly to cope with increased physical stress. β-Endorphin is also released as an important reliever of stress and pain, especially in overload and prolonged intense exercise [12].

Although a postexercise hypotensive response could last up to approximately 20 h after a single bout of endurance training [13], stress-induced physiological changes could draw excessive

burden on the cardiovascular system during heavy exercise, when markedly elevated systolic BP and accelerated HR are inevitable. As vascular resistance to skeletal muscles decreases during vigorous exercise, blood flow resistance to visceral organs increases, which could be a serious stress to the body. If this condition is sustained for a certain period, severe tissue ischemia may ensue.

Our previous study showed that cardiovascular burden remained high shortly after heavy exercise in young volunteers who had kept endurance training in gym facilities for months to years [6]. They also had a high incidence of large amounts of red blood cells on the urine routine, and transient but marked albumin-proteinuria was evident during heavy exercise.

Therefore, for safety consideration, moderate- and high-intensity exercises were not implemented in hypertensive subjects in the present single session or regular walking study. To find a relatively safe and feasible way of physical activity and to avoid the over-activation of the sympathetic system during exercise,

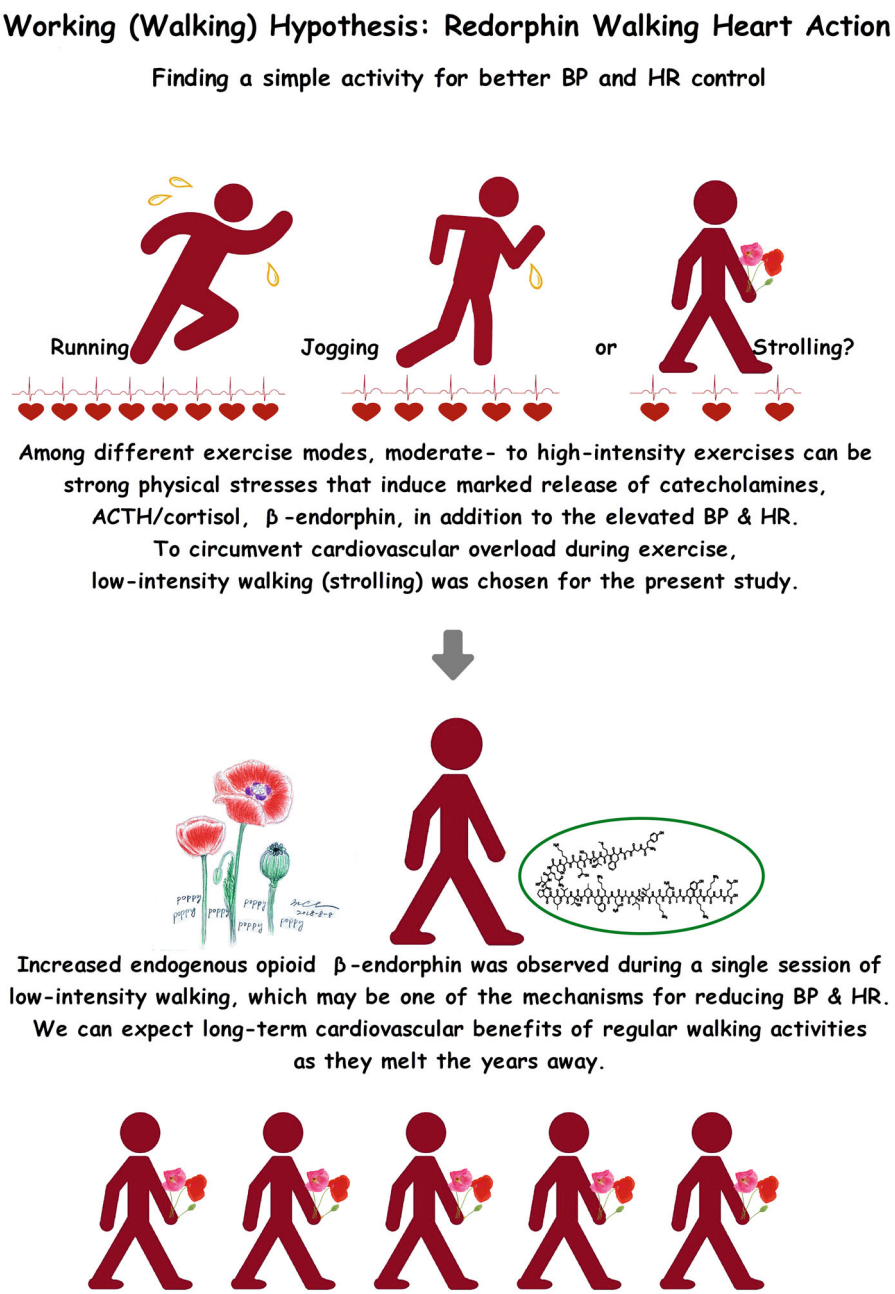

Fig. 2 Rationale of low-intensity exercise as medication in hypertensive subjects. BP, blood pressure; HR, heart rate; ACTH, adrenocorticotropic hormone; MET, metabolic equivalent of task. Redorphin indicates Regular Walking Heart Action Study with walking-induced endogenous opioid release (re + dorphin). Running and jogging figures represent respective high- and moderate-intensity exercise recommended by guidelines. Strolling figure represents low-intensity exercise that has been generally considered "ineffective" in the management of hypertension. Repetition of the electrocardiograph with heart symbol under exercising figures represents respective heart rate during exercises of various intensities. The circle with the chemical structure of β-endorphin inside indicates the release of endogenous opioids during different intensities of exercise including strolling. The poppy image indicates plant-originated opioids with effects of vasodilation and euphoria, similar to exercise-induced β-endorphin, which helps promote walking adherence and may in turn enhance compliance with exercise medication in hypertensive subjects and ameliorate drug dependence. The strolling figures in the last lane represent mild exercise that could be performed regularly at the population level in the daily life

only mild exercise, namely, low-intensity walking (<3 METs, low-MET walking), was prescribed for hypertensive subjects in our studies (Fig. 2).

The idea is that exercises of different intensities induce various adaptive changes in different systems and organs. Vigorous exercises, in many instances, can be both physical and mental stresses that activate the hypothalamus-pituitary-adrenal axis to release catecholamines and adrenocorticotropic hormone with subsequent hypertension and tachycardia in maladaptive individuals, which could not be antagonized completely by concomitant release of endogenous opioids. If a single session of low-MET walking could transiently enhance endogenous opioid release with little stress while inducing vasodilation and well-being (endorphin-induced euphoria), we can expect long-term cardiovascular benefits of regular walking activities as they melt the years away. Elevated β-endorphin also promotes exercise adherence, which in turn could enhance compliance with exercise in hypertensive subjects and thus reduce sitting time. Regular low-intensity exercise is also postulated to enhance the effects of anti-hypertensive drugs and to ameliorate drug dependence.

We are far from arriving at the final conclusion from the present results; however, if a single session of low-MET walking could enhance release of endogenous opioids, long-term regular implements of such mild exercise would also promote the endogenous release of blood pressure-lowering molecules, including β-endorphin. This is the main rationale for choosing low-intensity (low-MET) walking for hypertension management (Fig. 2).

Mechanisms whereby low-MET walking lowers blood pressure

Using the definition for a MET as the ratio of work metabolic rate to a standard resting metabolic rate of 1.0 (4.184 kJ)·kg^{-1}·h^{-1}, 1 MET is considered a resting metabolic rate obtained during quiet sitting. The walking speed of our study had an exercise intensity of 2-2.5 METs according to the criteria of exercise intensities [8]. Although the present exercise intensity did not meet that recommended by most guidelines, strolling for 3 km was of sufficient distance and duration with a total exercise volume of 150 METs·min (2.5 METs × 60 min), similar to that of a moderate-intensity exercise of 5 METs for 30 min recommended by guidelines. The total METs-time per week could reach 500–1000 METs·min/week if one does such mild walking for at least 5–7 times a week.

As in our previous study, such low-MET walking for 50–60 min showed a brief lowering of BP and HR with elevated β-endorphin in young volunteers [6], a slight, transient but clear hypotensive response along with a negative chronotropic response to a single session of 3-km low-MET walking was observed in all subgroups (hypertensive, prehypertensive and rapid HR groups) of the present study. When low-intensity exercise sustains for sufficient time, it may result in pressure-lowering through some similar mechanisms to that of moderate-intensity exercise, which are generally accepted.

Vigorous exercise causes vasodilation through various mechanisms, such as elevation of nitric oxide, carbon monoxide, prostaglandins, and β-endorphin as well as reduction of vessel-constricting transmitters and peptides. [7, 12–15] β-Endorphin, a neuropeptide consisting of 31 amino acids that were originally isolated from the pituitary gland and the hypothalamus, has been found in a variety of tissues and organs, including cardiomyocytes [12, 16]. Modern investigation has revealed that opioids have two well-established $G_i/_0$ protein-coupled actions on neurons: they close voltage-gated Ca^{2+} channels on presynaptic nerve terminals and thereby reduce transmitter release, and they open K^+ channels and hyperpolarize and thus inhibit postsynaptic neurons, including norepinephrine. With the effects of tranquilizing, mild vasodilating and HR inhibition in addition to analgesia, β-endorphin could act as a buffer against exercise-related sympathetic excitation and cardiovascular overload. Therefore, we proposed that the elevation of β-endorphin may also play a role in the pressure-lowering and negative chronotropic effects of low-MET walking.

Many participants reported warming up of extremities after low-intensity walking, indicating overall vasodilatation due to mild exercise, in contrast to runners' cold extremities due to vasoconstriction by large amounts of catecholamines. Because slow walking also involves most core skeletal muscles, the contraction and relaxation of these muscles promote vasodilating opioids and nitric oxide to circulate throughout the body, maintaining sufficient organ perfusion with less potential of overload on the heart.

The mechanisms of pressure-lowering of low-intensity walking for two months or longer periods may have similar components to that of one session walking. We monitored two volunteers who did slow walk for two consecutive years, and the transient elevation of urine endorphin after walking was always present with transient BP reduction in the same person. The other mechanisms of increased vasodilators, such as exercise-induced nitric oxide and carbon monoxide, as well as decreased sympathetic activity, improved baroreflex function, and renin-angiotensin system may be involved in the pressure-lowering effects of long-term exercise training of both low- or high-intensity exercise [7, 12–16]. In addition to vasodilation, heart-rate-lowering is also an important factor for cardiac output reduction and therefore blood pressure control, especially in long-term regular low-intensity walking. Although we could not arrive at the final conclusion from the present results, if a single session of 3-km low-MET walking could briefly reduce BP and HR, repeated implements of such low-MET exercise in our daily life would much likely add to promote pressure control with similar exercise-related mechanisms that were found in moderate- or high-intensity exercise, which surely warrant more research and verification.

Strengths and limitations of the present study

Mild exercise as walking at low speed in the present study is a pragmatic and feasible form of exercise medication with reduced potential for cardiovascular overload. It should be accessible for hypertensive subjects and other individuals who find it difficult to engage in moderate or vigorous exercise. The methods used in the present study were noninvasive, and the cardiovascular and exercise data collected were not self-reported but were obtained by trained researchers. The research subjects in the regular walking study were trained for walking method for at least twice and supervised by trained investigators at regular visits.

Because a slow 30-min walk twice daily also showed beneficial effects on BP and HR, it may be an appropriate approach for frail people with chronic illness [17]. The results of a regular walking study imply a cumulated dose-response effect of low-intensity exercise, although the sample size is too small to draw a definite conclusion up to now.

Although the exercise intensity of the present study did not meet guideline recommendations, the sufficient walking distance, duration and frequency of low-intensity walking (i.e., up to 3 km and 60 min/d, 5–7 times/week) could be complementary to the BP- and HR-lowering doses. In the new 2017 ACC/AHA guideline for the prevention and management of high blood pressure, they recognized the evidence that even modest sustained lifestyle changes such as walking to work could substantially reduce cardiovascular morbidity and mortality [2, 18]. In addition, some studies found that a "weekend warrior" regimen and other leisure-time physical activities that did not meet the guidelines also reduced the risk of all-cause and cardiovascular mortality [19]. In

addition, low-intensity walking costs little, the present variables tested are noninvasive, and it may be a priority choice to increase the compliance of exercise therapy in hypertensive populations.

When prescribing exercise to hypertensive individuals, it is also important to avoid exercise-related lesions to the musculoskeletal system as well as the cardiovascular system and other organs, such as the kidney. We found that long-term high volume running in normal rats enhanced vessel inflammation and impaired endothelium-dependent vasodilation with elevated BP [20]. The newly published Dementia And Physical Activity (DAPA) trial of exercise training for people with mild to moderate dementia also revealed that moderate- to high-intensity training programs did not improve cognitive impairment or even might worsen it [21]. Our recent study found that young students undergoing high-intensity endurance training in gym showed frequent blood urine and proteinuria in addition to a higher cardiovascular burden [6]. Therefore, safety and fewer side effects should be considered when prescribing exercise for frail or complicated hypertensive subjects.

We have not yet measured the levels of catecholamines and other stress-related hormones to further determine the sympathetic activity and stress level. Whether the elevated β-endorphin during mild exercise could reduce norepinephrine release and thus add to vasodilation and negative chronotropy needs to be determined. β-Endorphin is also reported to promote water and salt retention, but whether it can reduce ACTH/cortisol remains to be studied.

The small sample size in the present regular walking study did not allow us to postulate the long-term effectiveness of low-intensity walking in all hypertensive populations. That the number of people who decline to participate in low-intensity walking is high in practice is a major difficulty to circumvent. Simply giving information about the benefits does not appear to be effective in increasing participation in low-intensity walking. It is important to give feedback to encourage more hypertensive subjects to take part in regular walking to achieve the possible long-term benefits. The hypertensive subjects who hope to adopt nondrug therapies are potential populations to adopt such mild exercise. A low-intensity walk is also a cost-effective exercise mode to improve cardiovascular health and well-being, in addition to the cost of time. However, to save time, people could also contemplate on their daily life and work during slow walking at adequate venue under pleasant mood.

In conclusion, we found in a limited sample size that low-intensity walking with sufficient distance and duration could lower blood pressure and heart rate. The effectiveness of low-intensity exercise, its dosage and safety, its potential benefits with drug combination, and the underlying mechanisms of blood pressure control and/or other health problems such as diabetes, mental health, and joint protection merit intensive investigations.

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ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

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