



Research Article

Treating Blood Hypertension in a Brazilian Community: Moving from Reactive Homeostatic Model to Proactive Allostatic Healthcare

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Abstract

The responsiveness of hypertensive subjects to different types of physical exercises and length of intervention, has been investigated in samples of our dynamic cohort study ("Move for Health" program) based on spontaneous demand for healthy lifestyle with supervised exercises and dietary counseling. After clinical selection and baseline assessments they were spontaneously assigned to exercise protocols of strength (PAC) isolated or combined with endurance (walking) exercises (PMi) daily or in alternated days (PMiA), hydrogymnastics (PHY) and tread mill high-intensity exercises (PHit), applied during 10 (experiment 1) and 20 (experiment 2) weeks of intervention. Baseline demographic, socioeconomic, anthropometric and physical activity and fitness characteristics were similar among protocols. Ten-week training improved VO2max. Similarly in all protocols while hand grip increased only in PAC. In average, there was a 16% reduction rate of hypertension rate from baseline with both, SBP and DBP, reduced by PHY and only SBP by the PMi. After adjustments hypertension was more reduced by PAC, PMi and PHY. In the 20-week experiment, higher SBP was similarly reduced by PAC or PMiA and DBP by PMiA, after adjustments. Hence, so far, our generated data suggest physical exercises as an effective tool for hypertension reduction, from 10 weeks to 3 year-long supervised protocols composed by surface or aquatic activities with strength or endurance exercises. PAC takes longer and short-period responsiveness can be achieved by either combined (strength-endurance) or hydrogymnastic exercises. Thus, exercise training is a time- and type-dependent tool, feasible, costless and scientific-based rheostatic-allostatic alternative for the current "sick-care" drug-dependent homeostatic approach to hypertension med care.

Introduction

High blood pressure (HBP) is a strong, independent and etiologically relevant risk factor for cardiovascular and therefore, the leading cause of preventable deaths worldwide [1]. Roughly one-quarter of US adults are hypertensive (blood pressure >140/80 mm Hg on repeated measurement) and 95% are classified as "essential" hypertension [2]. Projections are that by the year of 2025, 75.0% (or 1.17 billion people) of the people with hypertension in the world will be living in emerging nations [3]. It is estimated that about one-third of the population in Latin America is affected by Blood Hypertension. Baseline findings (2014) from ELSA-Brasil show a frequency of 35.8% high blood pressure [4]. Hypertension has high medical and social costs, primary due to its many associated complications which lead to more severe cardiovascular disease, mortality, morbidity, incapacity and the use of medical services worldwide, factors that create high costs [5]. The Brazilian Public Health System is free and universal that intends to provide health care free of charge to its



whole population. Since 1990 it has been organized by the Unified Health System (SUS-Sistema Unico de Saude) and the Family Health Strategy (ESF) was introduced in 1994, aiming to reorganize primary health care through the implementation of multi-disciplinary professional teams. The strategy aims to rationalize the use of all levels of assistance (primary, secondary and tertiary) [6]. The free distribution of medicines occurs since 1971. The distribution of more than 15 medications for HyPERtension and DIABetes (HIPERDIA program, begun in 2001), and the governmental fueling pharmaceutical-care expansion, clearly shows the important role of drugs in the Brazilian Government's effort to tackle these two diseases [7,8]. In Brazil, the cost of medication spent with either one (US\$ 87.10), two (US\$ 159.00) or three (US\$ 194.00) drugs averaged US\$ 39.50/month for each diagnosed hypertensive subject [9]. The estimated direct cost of hypertension treatment in this country is 1.46 times higher in public than the private system. Together they represented 0.08% of the GDP (in 2005), or 1.11% of overall health care costs [10]. Data sources on HiperDia Program are controlled mostly by the Ministry of Health and the available data are fragmentary and often outdated [8]. When looking at the effectiveness scale it is unquestionable that prevalence of diabetes and hypertension are still rising [11]. From 2006 to 2010, according to VIGITEL, the self-reported prevalence of diabetes increased 5.3% in 2006 to 6.3% in 2010, leading to an approximate 20% increase [7]. Hypertension is estimated to present a 60% increase by the year 2025. Projections are that by the year of 2025, 75.0% (or 1.17 billion people) of the people with hypertension in the world will be living in emerging nations [12]. Thus seems that besides onerous, the SUS care of HyPERtension and DIABetes has been demonstrated as ineffective. It is known that therapy is the attempted remediation of a health problem following a diagnosis. In the case of hypertension seems that is having a lacking of both, lack of real aknowledge of the health problem (disease) and/or misinterpretation of the blood pressure variation, by the caregiver professional.

Knowing epigenetics of blood pressure variation

Elevated blood pressure results from environmental factors, genetic factors, and interactions among these factors [13]. Our ancestors were often faced with survival stresses, including famine, infection and water and sodium deprivation. As results of natural selection, the survival pressures drove our evolution to shape a thrifty genotype, which favored/ promoted energy-saving and sodium/water preservation. However, with the switch to a sodium- and energy-rich diets and sedentary lifestyle, the thrifty genotype and ancient frugal alleles, are no longer advantageous, and may be maladaptive to disease phenotype, resulting in hypertension, obesity and insulin resistance syndrome [1,14-16]. Particularly on the blood pressure control, our ancestors were faced with the hot and humid climate, like in eastern Africa. Effective heat dissipation is essential in hot environments and is achieved most efficiently through evaporative heat loss [17]. However, sweating due to the hot climate and excessive labor activities can lead to a large loss in the amount of salt and water, and eventually lead to hypovolemia, a threat to human survival. In addition, human and nonhuman primates living in ancient times had very low salt intake available. Low salt intake and large salt losses due to sweating had created robust salt appetite and renal sodium conservation, which were essential to survival [18]. Water loss and sodium deprivation due to insufficient sodium intake or excess sodium loss may activate rennin-angiotensin-aldosterone system, sympathetic nerve or neuroendocrine system to preserve sodium. The accumulation of sodium in tissue is accompanied by a commensurate retention of water to maintain the isotonicity of body fluids [18]. And, consequently, maintaining blood pressure [19]. Moreover, by facing infection, trauma and physical stress [20], there was an activation of the innate and adaptive immune system and, the acute inflammatory episode may cause water loss. Hence, to cope with the injury responses, a coordination of neuroendocrine, energy storage, water economy and immune systems are adapted. Some hormones that mediate water retention such as angiotensin II and aldosterone are also endowed with pro-inflammatory effects, and has an important



role in the pathogenesis of hypertensive and metabolic diseases. Moreover, immune cells, such as mononuclear phagocyte system and macrophages, are responsible for interstitial hypertonic sodium retention, resulting from high salt diet intake, and stimulate lymph-capillary network formation. Notably, neoformed vessels (angiogenesis) in skin may serve as an extra sodium and water storage to buffer extra-cellular volume expansion and maintenance of blood pressure homeostasis. Hence, immune system plays some role in the regulation of sodium and water homeostasis [21]. Additionally, inflammatory cytokines released from activated immune cells inhibits insulin signaling pathway. In addition to its metabolic effects, insulin induces vaso- relaxation and regulates sodium homeostasis by enhancing sodium reabsorption in the kidney, thereby, contributing to the regulation of blood pressure [18,22]. Thus, the increased blood pressure by insulin resistance may contribute to increased blood perfusion to the brain during starvation and infection, and to the fetus during pregnancy [23]. Therefore, negative regulation of insulin signaling could be viewed as a physiologic ‘adaptive mechanism’ that is activated in certain conditions such as fasting, inflammation, stress and pregnancy [18,22]. Because organisms adapt to the totality of their environment, or ecological niche, it is hypothetically possible that natural selection favors organisms harboring the genotype for a metabolic system [18]. Thereby, as results of natural selection, the survival pressures drove our evolution to shape a thrifty genotype, which favored/promoted energy-saving and sodium/water preservation [24]. Though, at least two genes: angiotensinogen (AGT) and the epithelial sodium channel γ subunit (ENaC γ), are involved in the regulation of sodium and blood pressure homeostasis [25]. However, this natural selection of thrifty genotype, which was a physiological adaptive mechanism for human survival, on the current environment, is maladaptive to disease phenotype [18,20,23,26]. As such, salt- sensitive hypertension sodium-conserving (thrifty) genotype may be maladaptive to the modern environment of sodium abundance [24]. Thus, epigenetic high blood pressure results from the mismatch of our ancestral thrifty genotype which favored/promoted energy-saving and sodium/water preservation, with a contemporary sodium- and energy-rich diets and sedentary lifestyle environment [14].

Knowing the target of treatment

Man and animals are exposed to a large number of biological and environmental factors (stressors) like alterations in feed and husbandry practices, climatic variables, transportation, regrouping, the therapeutic and prophylactic activities etc. The ability of the man and animal to fight against these factors is important for maintenance of their health and productivity [27]. The presence of a stressor leads to the activation of neurohormonal regulatory mechanisms of the body, through which it maintains the homeostasis [28]. Homeostasis is the property of a system within the body in which a variable is actively regulated to remain very nearly constant. Though, homeostasis is the regulation of the body to a balance, by single point tuning. The homeostatic regulation occurs despite changes in the animal’s environment, or what it has eaten, or what it is doing (for example, resting or exercising). Each of these variables is controlled by a separate “homeostat” (or regulator), which, together, maintain life. Homeostats are energy-consuming physiological mechanisms. On the other hand, allostasis is the process of achieving stability through physiological or behavioral change. The concept of allostasis, maintaining stability through change, is a fundamental process through which organisms actively adjust to both predictable and unpredictable events [29]. This can be carried out by means of alteration in HPA axis hormones, the autonomic nervous system, cytokines, or a number of other systems, and is generally adaptive in the short term [30]. Both homeostasis and allostasis are endogenous systems responsible for maintaining the internal stability of an organism [27] as well, both respond to stressors motivated by stress. Stress can be defined as a process of altered biochemical homeostasis produced by psychological, physiological, or environmental stressors [28]. On the basis of duration and onset, stress might be acute and chronic and generally released with the removal of cause.



Homeostasis describes mechanisms that hold constant a controlled variable by sensing its deviation from a “setpoint” and feeding back to correct the error. Consequently physicians design therapies to restore the “inappropriate” value to “normal”. However, in medicine, major diseases now rise in prevalence, such as essential hypertension and type 2 diabetes, whose causes the homeostasis model cannot explain [31]. Pressure spends about equal time above and below the steady daytime level. This pattern suggests, not defense of a setpoint, but rather responsiveness to rising and falling demand. Once the brain predicts the most likely demand, it resets the blood pressure to match. To do so, the brain directly modulates all three primary effectors: nerves signal the heart to pump faster, blood vessels to constrict, and kidneys to retain salt and water. These direct neural messages are reinforced by additional signals acting in parallel. For example, the neural system that excites the primary effectors also releases multiple hormones that send them same message. Hormones signaling the opposite message are suppressed. This pattern: multiple, mutually reinforcing signals acting on multiple, mutually reinforcing effectors, overrides the various feedbacks that oppose change. Recognizing such fluctuation, it has been proposed the idea of shifting setpoints termed, “rheostasis”. Essentially all biological parameters fluctuate with different amplitudes and time constants, and these fluctuations all share a single goal. Yet the goal is not constancy, but coordinated variation to optimize performance at the least cost. This is the core idea of allostasis [31].

The allostasis approach to hypertension

The homeostasis model cannot explain essential hypertension because it attributes all pathology to a “defect”-to something “broken”. But the allostasis model suggests that there is no defect. More parsimoniously, it proposes that hypertension emerges as the concerted response of multiple neural effectors to prediction of a need for vigilance. When this prediction is sustained, all the effectors, both somatic and neural, adapt progressively to life at high pressure [31]. The neural signals that call for increased blood pressure also call for salty foods-which the fast-food industry (“industrial agriculture”) provides in prodigious quantity. Industrial agriculture does not cause hypertension by excessively salting prepared foods; it merely obliges the public’s appetite for sodium, which is driven quite appropriately by intact regulatory systems. Indeed, if under present conditions of life, the food industry were to restrict sodium, we might see the development of public “salt licks” [31]. Vigilance starts when a child is delivered from its mother’s protection to the care of strangers. In a younger person if the predicted need for vigilance declines, effector adaptations can reverse promptly. But persistent demand leads to more profound and persistent effector adaptations. Over decades the constant call for vigilance adapts arterial muscle and carotid sinus to thicken and stiffen so that pressure rarely returns to normal levels [31].

Probably there are also corresponding adaptations in the brain. We know now that adult synapses continuously adjust their molecular components and that “memories” are stored at all levels, even in the spinal cord [32-33]. So the many hormones that feed back to the brain to sustain high pressure probably entrain many levels to expect and support high pressure. Thus, coordinated somatic and brain adaptations generate response patterns of “established” hypertension. The hypertensive pattern, like the normal pattern, does not seem to be “defended” at a particular level. Rather it is modulated up and down, apparently according to demand, with an overall range of 140 points. This pattern suggests adaptation to chronic vigilance, and consistent with this the hypertensive pattern is absent in undisrupted preindustrial societies where children remain in contact with their parents and strangers are rare [34]. Established hypertension is most common in segments of modern society where family structure is most disrupted, where children are least protected, and where they are marked from birth for suspicion and various forms of ill-treatment. So to explain essential hypertension there is no need to postulate a “defect” in any particular regulatory pathway. Certainly hypertension state might be created by mutation of one gene or another (Wilson et al., 2001). But we can also create hypertension and atherosclerosis in a whole colony of mice simply by introducing a stranger [35].



Certainly we recognize that the variance of blood pressure within a community must be partially caused by genetic differences. But this cannot explain why blood pressures of essentially all our children rise with age. Nor why the rise is largest and most persistent in the poorest and most socially disrupted communities. Nor why African-Americans are more hypertensive than genetically similar populations in West Africa. These observations certainly point to an environmental cause [31]. In summary, the allostasis model attributes the pathogenesis of hypertension to prolonged adaptation to hypervigilance and hyposatisfaction. The impact is strongest among populations with the best reasons for vigilance, the narrowest range of satisfactions, and expectations that are least often met [31].

Knowing the rational therapeutics

For responsiveness to rising and falling demand of blood the brain predicts the most likely demand, and resets the blood pressure to match. To do so, the brain directly modulates all three primary effectors: nerves signal the heart to pump faster, blood vessels to constrict, and kidneys to retain salt and water. Once diagnosed the hypertension, and following the homeostasis model, physicians try to restore each parameter to what they consider an “appropriate” level. Therefore, hypertension is treated with drugs that target the three primary effectors of elevated pressure: (i) diuretics to reduce blood volume; (ii) vasoconstrictor antagonists to dilate the vascular tree; (iii) heart rate antagonists to reduce cardiac output (Sterling, 2004). For so, the pharmaceutical industry continues to target myriad molecules that regulate these three mechanisms, and fundamental research widely promises to identify new targets. However, there are three problems with targeting low-level mechanisms. First, each signal evokes multiply cascaded effects, so even the most specific molecular antagonist will cause a cascade of effects. For example, in hypertension the angiotensin converting enzyme affects all of angiotensin’s myriad downstream targets (arteriolar muscle, kidney, and multiple brain sites), and so also does its widely prescribed inhibitor [31].

Second, the variables targeted for treatment are being driven to their particular levels by concerted signals from the brain in response to predicted needs. Consequently, if one signal is suppressed by a drug, the brain compensates by driving all the others harder. Thus, when blood pressure is treated by a diuretic to reduce volume, there are compensatory increases in heart rate and vasoconstriction. These can be treated in turn by beta- adrenergic antagonists, calcium channel antagonists, etc. [34,36].

Third, there is a cost to performance in clamping a variable to some target level by blocking the effectors designed to modulate it. Clamping renders that variable insensitive to predicted need, which opposes the whole point of physiological regulation. Thus clamping blood pressure low with a beta-blocker commonly causes “exercise intolerance”-inability to increase cardiac output when it is needed [31].

A more rational goal of intervention would be to shift the predicted distribution of demand back toward its original level. This would allow the effectors to naturally reestablish flexible variation around the predicted lower demand, thus preserving the range of responsiveness. In other words, by rational therapy, when demand is reduced for long periods, the system re-adapts to the initial demand distribution. The mean response returns to its initial level while responsiveness is maintained [31].

This seems to work very much for hypertension while considering that the current authoritative recommendations for treatment are no longer drugs but: (i) weight loss; (ii) exercise; (iii) moderate alcohol consumption; (iv) diet reduced in sodium and fat and increased in calcium, potassium, and fiber; (v) cease smoking [36]. Particularly under the “DASH” study, it was found overall reductions in blood pressure “comparable to or greater than those usually seen with monotherapy (i.e., 1 drug) for stage 1 hypertension”. But as the DASH study notes, long-term health benefits “will



depend on the ability of people to make long-lasting dietary changes, including the consistent choice of lower- sodium foods” and “upon (their) increased availability” [37]. This requires, in effect, a sustained victory in the prefrontal cortex of abstract knowledge about what is “good for you” over all the unsatisfied appetites that cause the problem in the first place. The most successful interventions do not deny the sense of need. Rather, they find ways to satisfy it by enlarging positive social interactions and revivifying the sense of connectedness [31].

Purpose

Drug therapy has been largely unsuccessful in halting and reversing the hypertension epidemic and the epigenetics studies point out the prevalence of hypertension as perpetrated by lifestyle factors, such as poor dietary habits, physical inactivity, cigarette smoking/secondhand smoke and strongly associated with various sources of social distress. The plethora of used drugs that essentially attempt to substitute for a healthy lifestyle has resulted in failure and prohibitive cost. In the implementation of effective population-based strategies, diet and physical exercise are the pillars of treatment. In previous experiments we had shown aerobic supervised exercises of walking-jogging leading to hypertension decreasing in a 3-year follow up. SBP normalized earlier (4 mo.) than DBP (6 mo.), with 31.6% of the patients normalizing both at 8mo. Intervention [5]. Later on, in the same community but under 10-weeks of a mixed exercise protocol, there was a 8.5% decreasing in SBP hypertension and in 5.2% DBP [14]. Presently, we intend to add further informations regarding the hypertension responsiveness to protocols with different types of exercises interacting with short (10 weeks) and long (24 weeks) period of intervention.

Material and Methods

Subjects

Participants were enrolled at the “Move for Health Program” (*Programa Mexa-se Pró-Saúde*), an ongoing epidemiology project conducted, as extension-assistance of the university, since 1991. The program introduces healthy lifestyle into subject’s diary activities by promoting nutritional re-education and supervised physical exercise as primary care for chronic non-communicable diseases. As a community -based project it includes adult (>35 yrs old) participants from both genders that come to the clinic spontaneously or by either a friend or doctor indication looking for preventive health examination with further non-medicated interventions. Upon registration and accomplishing ethical requirements the subjects are submitted to multi professional assessments for clinical, anthropometric, dietary, physical activity, blood analysis, fitness (aerobic, strength and flexibility), and postural. From these baseline assessments the participants are able to choose follow-up interventions involving supervised exercises combined with weekly counseled (or supervised) dietary interventions (LiSM program). The follow-up assessments occur every 10 weeks. The assessments as well as physical exercises and dietary interventions are conducted by graduate students holding institutional fellowships. The program is opened for beginners three times a year and is free of charge for the first 10 weeks [15,38].

Measurements

Physical activity level (PAL), socio-demographic characteristics (gender, age, marital status, family income and education) and health status are obtained by applying the International Physical Activity Questionnaire (IPAQ version 8 - long form) [39]. Marital status was classified as married (married and stable union) and unmarried (single, widowed, divorced, and separated). The schooling level was classified as fundamental complete and incomplete, secondary education and higher. Family income ranked from up to five minimum wages (<5SM) or greater/equal to five times the minimum wage ($\geq 5SM$). Health perception was rated as good (excellent,

very good or good) or bad (fair and poor). Body weight and height measurements are taken [40] with subsequent calculation of body mass index ($BMI=kg/m^2$) classified as normal weight when up to $24.9 kg/m^2$, overweight 25 up to $29.9 kg/m^2$ and obese with values greater than $30 kg/m^2$ [41]. The waist circumference (WC) is measured with millimeter tape inextensible and inelastic on the midpoint between the last intercostal space and iliac crest. The value of 88 cm is adopted as cutoff for abdominal obesity [40]. Body muscle and fat composition is performed in the supine position by bioelectrical impedance (BIA) (Biodinâmics®, model 450, USA) with the calculation of muscle mass by the equation proposed by [42] calculated as body mass index (IMM) as proposed by [43]. Sarcopenia classification adopted for women was: Normal- $IMM>5.45kg/m^2$, Sarcopenia - $IMM \leq 5.45 kg/m^2$ [44]. The percentage of female fat used as normal is 20-35% [45].

Blood pressure

An initial medical screening is carried out to exclude those individuals with severe hypertension, diabetes mellitus, cardiopulmonary, renal, hepatic, and severe orthopedic diseases. The evaluation of the PA is held with the subject seated, following the recommendations of the VI Brazilian Guidelines on Hypertension (SBC, 2010). Resting blood pressure (BP) is measured using a digital automatic oscillometric device (Omron, USA). As published earlier [1,5], these measurements were superimposed to parallel measurements taken with a standard mercury manometer in the initial screening period and, there were no significant intra-and inter-device reading deviation.

Lifestyle modification protocol

Nutritional counseling is applied weekly through lectures in groups with relevant nutritional context in which subjects were comprised. Physical Exercises Protocols consisted by supervised exercise sessions in accordance with the ACSM's guidelines for exercise prescription and treatment of chronic non-communicable diseases [46].

Physical exercises protocols

1) Academy exercises (Pac) with elderly-adapted weight-lift equipments distributed in a circuit sequence. Each 60min. supervised- session was composed by 10min. dynamic- warm up/stretching, 40min. of resistance training (3 sets of 8-12 repetitions at 60%-70% 1RM each exercise) finishing up with 10min. cool down- stretching. The strength training sessions were preceded by 2wk-exercise familiarization and 1 RM test realization. Daily sessions were conducted three days a week, alternately.

2) Daily-Mixed Exercises (PMi): The physical exercise protocol is composed by daily sessions of 90 min, including 10min dynamic- warm up/ stretching, 30 min walking ($60-80\% VO_{2max}$), 40min strength in academy (3x 8-12 rep, 60-70% 1RM) and 10min stretching and cool down. Strength exercises were alternated in different days, for upper and lower limbs. Vo_{2max} . Is determined by the Balke's protocol in electronic treadmill [47]. The mixed-exercise protocol should be attended three or more sessions during the week.

3) Alternately concurrent exercises (PMiA): subjects were submitted to walking and stretching (aerobic activities, at Mondays, Wednesdays and Fridays) and resistance training (weight-lifting activities, Tuesdays and Thursdays).

4) HIT (PHit): The twice a week, 60min. whole exercise-protocol was composed by initial (5 minutes) and final (10 minutes) stretching; the latter was intended as an aid to cool down for baseline-heart rate recover. The 43min. high-intensity interval training on treadmill included 10 minutes of warm-up at 70% of maximum heart rate (HR max), followed by 4 series of 4 minutes each on 90% HR max with 3-min intervals between series for active recovery at 70 % of FC max. [48].

5) Hydrogymnastics (PHy): 60 minutes of exercise predominantly aerobic in a 29o.C swimming pool, compose by 10min. warm up, 10min. stretching, 30min. principal and ending up with 10min. slowing down towards heart rate stabilization. Exercises were conducted twice a week in alternated days.

Statistical Analysis

Results were expressed as mean and standard deviation for continuous variables and frequency and percentage for categorical variables. The proportion comparisons were done by chi-square test (χ^2), the ANOVA repeated measure for symmetric quantitative variables and the range model repeated measures for the asymmetric quantitative. SAS for Windows, version 9.1 was used with a significance level of 5% or corresponding p-value.

Results

Experiment 1

Sample composed by 606 individuals, aged 55.5 ± 10.8 years, 88% females, marrieds (88%), low-socioeconomic (92%) and elementary schooling (80%), consuming inadequate diet (95%), 91% referring the WHO (2010) recommended physical activity but with 80% overweight. Regarding the physical fitness the sample presented, at baseline, 63% good aerobic (VO_{2max}) and 78% good (hand-grip) strength fitness. The found hypertension rate was 41,4%. There were no differences among protocols for all these variables, at baseline (Table 1).

Table 1: General base-line characteristics of the sample in the physical-exercise protocols.

Variables/Protocols	PHy	PHit	PAc	PMi	TOTAL
Age (years)	60.2±10.4	53.3±8.8	57.5±12.7	53.4±10.2	55.5±10.8
<60	32 (50.8%)	36 (83.7%)	29 (58%)	98 (67.1%)	195 (64.6%)
≥60	31 (49.2%)	7 (16.3%)	21 (42%)	48 (32.9%)	107 (35.4%)
Gender					
Female	62 (98.4%)	43 (100%)	39 (78%)	122 (83.5%)	266 (88.1%)
Male	1 (1.6%)	0 (0%)	11 (22%)	24 (16.5%)	36 (11.9%)
Marital status					
Married	54 (85.7%)	34 (79.1%)	43 (86%)	110 (75.3%)	241 (79.8%)
Non-married	9 (14.3%)	9 (20.9%)	7 (14%)	36 (24.7%)	61 (20.2%)
Family income					
Up to 5 minimum wage	60 (95.2%)	38 (88.4%)	41 (82%)	140 (95.9%)	279 (92.4%)
>5 minimum wage	3 (4.8%)	5 (11.6%)	9 (18%)	6 (4.1%)	23 (7.6%)
Schooling					
Elementary	55 (87.3%)	36 (83.7%)	40 (80%)	110 (75.3%)	241 (79.8%)
High school/college	8 (12.7%)	7 (16.3%)	10 (20%)	36 (24.7%)	61 (20.2%)
Health Eating Index					
Inadequate	38 (100%)	26 (96.3%)	30 (90.9%)	118 (94.4%)	212 (95.1%)
Adequate	0 (0%)	1 (3.7%)	3 (9.1%)	7 (5.6%)	11 (4.9%)
Body weight					
Overweight	54 (85.7%)	36 (83.7%)	36 (72%)	117 (80.1%)	243 (80.5%)
Eutrophy	9 (14.3%)	7 (16.3%)	14 (28%)	29 (19.9%)	59 (19.5%)
Physical activity level					
Recommended	58 (92.1%)	41 (95.4%)	44 (88%)	132 (90.4%)	275 (91.1%)
Lower than recommended	5 (7.9%)	2 (4.6%)	6 (12%)	14 (9.6%)	27 (8.9%)
Hand grip strength					
Low	15 (23.8%)	5 (11.6%)	10 (20%)	37 (25.3%)	67 (22.2%)
Good	48 (76.2%)	38 (88.4%)	40 (80%)	109 (74.7%)	235 (77.8%)
Cardiorespiratory fitness					
Low	4 (25%)	7 (21.9%)	6 (50%)	20 (51.3%)	37 (37.4%)
Good	12 (75%)	25 (78.1%)	6 (50%)	19 (48.7%)	62 (62.6%)

Mean±_SD, PHy=hydrogymnastic; PHit=treadmill high intensity; PAc=academy; PMi=mixed academy/endurance exercises



The characteristics of the used protocols are in table 2. All protocols were considered as the moderate intensity. Only PMi was longer-length than the others, consequently offered higher volume and energy expenditure than the others.

Ten-wk exercise training improved VO2max. Similarly in all protocols while hand grip increased only in PAc. The average SBP and DBP were both reduced by PHy and only SBP by the PMi (Table 3). Overall, hypertension rate was reduced from 41,4% to 25,5%.

Analysis of categorized variables showed, after all adjustments that hypertension rate was reduced by the protocols PAc, PMi and PHy (Table 4).

Experiment 2

Baseline data from 124 subjects enrolled to the Move for Health program during the 2011-2012 period fulfilled the inclusion criteria for this experiment. Sample was predominantly female (81.5%), 84.7% overweight (50% obese), 27.4% hypertensive. The distribution among protocols was similar for the studied variables (Table 5).

After the 24wk intervention the hypertension rate was reduced by 21.3% in the PMiA, 18.8% in the PHy and 16.6% in the PAc. The SBP was reduced similarly, by protocols PAc(9.4 mmHg) and PMiA(6.3 mmHg) whose effects were maintained after the adjustments for the confounded variables(Table 6). The DBP was reduced (5.6 mmHg) only by PMiA, under all adjustment conditions (Table 7).

Table 2: The characteristics of the used protocols.

Variables/Protocols	PHy	PHit	PAc	PMi
Session (minutes)	60	60	60	90
Week frequency (day/week)	2	2	3	3 a 5
Intensity	Moderate	Moderate/Vigorous	Moderate	Moderate
Total Volume (min/week)	120	120	180	270 to 450
Energy Expenditure (METs/session)*	200	248.1	272.5	371.5

PHy=hydrogymnastic; PHit=treadmill high intensity; PAc=academy; PMi=mixed academy/endurance exercises; *Ainsworth et al. [53].

Table 3: The effects of 10-wk intervention with different protocols of physical exercises.

Variables		Exercise Protocols			
		PHy	PHit	PAc	PMi
Hand grip strength(kg)	M0	26.1±6.5 aB	29.5±6.0 aA	31.7±12.9 aA	29.6±10.6 aA
	M1	26.4±6.7 aB	29.9±5.9 aC	34.6±13.3 bA	31.2±10.0 bAC
VO2max (ml/kg/min)	M0	27.9±5.2 aA	32.3±5.4 aB	31.8±8.9 aAB	29.9±5.9 aAB
	M1	32.7±4.9 bA	37.2±5.9 bB	35.1±9.2 bAB	33.5±6.2 bA
SBP (mmHg)	M0	127.6±16.5 aA	117.6±12.9 aB	121.9±15 aABC	122.6±17.4 aC
	M1	121.2±17.9 bA	118.2±14.8 aA	120.1±16.8 aA	120.0±15.3 bA
DBP (mmHg)	M0	80.4±11.1 aA	74.8±11.7 aB	77.9±10.6 aAB	78.4±1.6 aAB
	M1	79.1±13.2 aA	75.7±11.7 aAB	76.3±11.1 aAB	75.6±10.1 bB

Mean±_SD, PHy=hydrogymnastic; PHit=treadmill high intensity; PAc=academy; PMi=mixed academy/endurance exercises; Mo=baseline; M1=after 10 weeks; SBP=systolic blood pressure; DBP=diastolic blood pressure.

Table 4: Effects of 10w-protocols on the hypertension rate.

	PHy			PHit			PAc			PMi		
	M0	M1	p	M0	M1	p	M0	M1	p	M0	M1	p
Blood pressure												
High	36 (57.1%)	20 (31.8%)	0.004	8 (18.6%)	9 (20.9%)	0.78	18 (36%)	9 (18%)	0.04	63 (43.2%)	39 (26.7%)	0.003
Normal	27 (42.9%)	43 (68.2%)		35 (81.4%)	34 (79.1%)		32 (64%)	41 (82%)		83 (56.8%)	107 (73.3%)	
	N=63	N=63		N=43	N=43		N=50	N=50		N=146	N=146	

Phy=hydrogymnastic; PHit=treadmill high intensity; PAc=academy; PMi=mixed academy/endurance exercises; M0=baseline; M1=after 10 weeks.



Table 5: Age, anthropometric and vascular variables distribution among physical-exercises protocols.

	PAc (n=24)	PMiA (n=75)	PMi (n=9)	PHy (n=16)	p valor
Age (yrs)	55.0±11.1	52.7±9.0	49.0±8.0	58.4±10.5	0.0728
Body wt (kg)	79.0±17.5	79.7±21.3	84.6±17.2	76.6±15.9	0.8088
Height (m)	1.63±0.1	1.59±0.1	1.62±0.1	1.61±0.1	0.1597
BMI	28.9±5.1	31.5±6.8	32.1±5.7	29.6±6.2	0.2246
WC	97.3±11.5	98.6±17.0	99.2±11.5	95.0±15.7	0.8477
%BF	32.7±9.5	36.7±10.5	36.7±9.2	37.6±10.5	0.2628
MM	24.2±7.5	20.5±4.2	21.8±5.9	21.9±4.4	0.1976
MMI	9.0±2.1	7.9±1.2	8.5±1.6	8.3±1.0	0.2456
SBP	126.0±16.0	122.1±16.5	124.0±16.0	122.9±10.5	0.8572
DBP	80.6±11.2	78.6±11.4	79.0±10.5	83.1±11.3	0.6748

Mean±_SD, PHy=hydrogymnastic; PAc=academy; PMi=daily mixed=academy/endurance exercises; PMiA=PMi alternating days for academy and endurance; Mo=baseline; M1=after 10 weeks; SBP=systolic blood pressure; DBP=diastolic blood pressure; BMI=body mass index; %BF=% body fat; MM=muscle mass; MMI=muscle mass index; wc=waist circumference.

Table 6: Regression analysis of the categorized variables of systolic blood pressure in each exercise protocol after 10 weeks of intervention.

Model		PAc	PMiA	PMi	PHy
1	M0	126.0±16.0aA	125.0±16.0aA	122.9±10.5aA	122.1±16.5aA
	M1	116.6±14.1bA	118.7±10.8bA	121.6±17.2aA	121.9±10.8aA
2	M0	126.0±16.0aA	125.0±16.0aA	122.9±10.5aA	122.1±16.5aA
	M1	116.6±14.1bA	118.6±10.8bA	121.6±17.2aA	121.9±10.8aA
3	M0	126.0±16.0aA	121.9±10.8aA	122.9±10.5aA	122.1±16.5aA
	M1	116.6±14.1bA	118.6±10.8bA	121.6±17.2aA	121.9±10.8aA
4	M0	126.0±16.0aA	125.0±16.0aA	122.9±10.5aA	122.1±16.5aA
	M1	116.6±14.1bA	118.6±10.8bA	121.6±17.2aA	121.9±10.8aA
5	M0	126.0±16.0aA	125.0±16.0aA	122.9±10.5aA	122.1±16.5aA
	M1	116.6±14.1bA	118.6±10.8bA	121.6±17.2aA	121.9±10.8aA
6	M0	126.0±16.0aA	125.0±16.0aA	122.9±10.5aA	122.1±16.5aA
	M1	116.6±14.1bA	118.6±10.8bA	121.6±17.2aA	121.9±10.8aA
7	M0	126.0±16.0aA	125.0±16.0aA	122.9±10.5aA	122.1±16.5aA
	M1	116.6±14.1bA	118.6±10.8bA	121.6±17.2aA	121.9±10.8aA

Mo=baseline; M1=after 10 wks;a,b: p<0.05 M0xM1; A,B,C :p<0.05 among protocols; Model 1=crude; Model 2=adjusted for age and gender; Model 3=model 2+body mass index; Model 4=model 3+waist circumference; Model 5=adjusted for age, gender and muscle mass; Model 6=model 5+body mass index; Model 7=adjusted for age, gender, muscle mass and waist circumference.

Table 7: Regression analysis of the categorized variables of diastolic blood pressure in each exercise protocol after 10 weeks of intervention.

Model		PAc	PMiA	PMi	PHy
1	M0	80.6±11.2aA	79.0±10.5aA	83.1±11.3aA	78.6±11.4aA
	M1	77.0±8.4aA	73.4±8.0bA	84.0±7.9aB	76.0±9.8aA
2	M0	80.6±11.2aA	79.0±10.5aA	83.1±11.3aA	78.6±11.4aA
	M1	77.9±8.4aA	73.4±8.0bA	84.0±7.9aB	76.0±9.8aA
3	M0	80.6±11.2aA	76.0±9.8aA	83.1±11.3aA	78.6±11.4aA
	M1	77.0±8.4aA	73.4±8.0bB	84.0±7.9aC	76.0±9.8aABC
4	M0	80.6±11.2aA	79.0±10.5aA	83.1±11.3aA	78.6±11.4aA
	M1	77.0±8.4aA	73.4±8.0bB	84.0±7.9aC	76.0±9.8aAB
5	M0	80.6±11.2aA	79.0±10.5aA	83.1±11.3aA	78.6±11.4aA
	M1	77.0±8.4aA	73.4±8.0bA	84.0±7.9aB	76.0±9.8aA
6	M0	80.6±11.2aA	79.0±10.5aA	83.1±11.3aA	78.6±11.4aA
	M1	77.0±8.4aA	73.4±8.0bB	84.0±7.9aA	76.0±9.8aAB
7	M0	80.6±11.2aA	79.0±10.5aA	83.1±11.3aA	78.6±11.4aA
	M1	77.0±8.4aA	73.4±8.0bB	84.0±7.9aC	76.0±9.8aAB

Mo=baseline; M1=after 10 wks;a,b: p<0.05 M0xM1; A,B,C :p<0.05 among protocols; Model 1=crude; Model 2=adjusted for age and gender; Model 3=model 2+body mass index; Model 4=model 3+waist circumference; Model 5=adjusted for age, gender and muscle mass; Model 6=model 5+body mass index; Model 7=adjusted for age, gender, muscle mass and waist circumference.



Discussion

The adult population sampled here lived in a middle size city in the richest state of the nation therefore, fully accessed to the SUS System and additionally, all having the health privileges for being domiciled under the umbrella of a local Public Medical School. Even though, the found undiagnosed hypertension was 9.8% [14] and the prevalence of hypertension varied from 28%(experiment 2)), 42%(experiment 1)), 51.2%[14] to 61.3% [5] by using clinical setpoints of SBP >_140mmHG and DBP >_90mmHg.

In 2002, the distribution of hypertensive patients by the Brazilian guidelines varied from 53.3% stage 1 to 35.7% stage 2 and 11% stage 3 [49]. In 2014, baseline findings from ELSA-Brasil study show a frequency of 35.8% high blood pressure [4]. The free demand probably would explain why our higher prevalence, comparatively to the general population. Afterall, as a chronic disease, hypertension is “silent”, slow in its progress and long in its continuance”. Our undiagnosed hypertension rate was 9.8% [14].

The diagnosis of hypertension by the high blood pressure “setpoint” follows the homeostasis model [31]. By decreasing the hypertensive setpoint policy from the clinical 140x90 mmHg to a recommended 130x 85 mmHg(NCEP-ATP III) or the recently recommended 120x 80 mmHg(that would increase hypertension rate by 5%), it accomplishes the goal of the “industry of the disease” by terrorizing the population to be medicated earlier by prescribers and , therefore, increasing the consume of pharmaceutical-industrialized drugs (NCEP ATP III, 2002).

Medication cannot be preventive, so it must follow clinical signs. Hypertension, as chronic disease, does not cross the “clinical horizon” so, it is not clinically manifested, during the natural course of the disease. Consequently, the reaction of the biomedical establishment has primarily been to apply modern technologies to stabilize overt clinical problems (e.g., secondary and tertiary prevention) [50].

The homeostasis definition of holding constant a controlled variable by sensing its deviation from a “setpoint” and feeding back to correct the error, has dominated physiology and medicine since Claude Bernard declared: “All the vital mechanisms... have only one object - to preserve constant the conditions of ... the internal environment”. There since, homeostasis model has contributed immeasurably to the theory and practice of scientific medicine [31].

By treating hypertension with drugs that target the three primary effectors of elevated pressure renders that variable insensitive to predicted need, which opposes the whole point of physiological regulation. For these reasons, less than 25% of hypertensive patients in the US are controlled. The major problem is considered to be “the very high rate of discontinuance or change in medications: 50-70% ... within the first six months... “[36]. These high discontinuance rates are considered to reflect, among other factors, “a combination of adverse drug effects, cost of drugs, and poor efficacy” [36]. Consequently despite their remarkable ingenuity, 30 years of low-level pharmacological treatments for hypertension have not worked [31]. The proportion of medicated non-controlled hypertension was 28.8% [14].

Definitely, homeostasis model cannot explain essential hypertension because it attributes all pathology to a “defect”. Someway differently, the allostasis model suggests that there is no defect. More parsimoniously, it proposes that hypertension emerges as the concerted response of multiple neural effectors to prediction of a need for vigilance. When this prediction is sustained, all the effectors, both somatic and neural, adapt progressively to life at high pressure. Thus, over decades the constant call for vigilance adapts arterial muscle and carotid sinus to thicken and stiffen so that pressure rarely returns to normal levels [31].



In our studies about possible vigilance factors on hypertension we have not found the socioeconomic characteristics of lower schooling and low income. These effects might be minimized by the fact that, in Brazil, the medication is free of charge. Moreover, our medical Institution conducts a specific program to attend all registered hypertensive subjects providing anti-hypertensive drugs. Thereby, it is hard to understand why 9.8% of the hypertensive patients were unaware of their abnormality (undiagnosed hypertension). On the other hand, lower schooling and socioeconomic status might influence food intake and, dietary quality that was proved as strong determinant of blood hypertension with higher blood pressure being associated with a dietary characteristics of high “processed pattern” (high sodium, low potassium and calcium, high sugar, low fiber) [14].

The unexpected high rate of medicated-non controlled hypertensive subjects leads to the hypothesis that anti-hypertensive drugs were not working reasonably and their users were not satisfied with them. Therefore, one might speculate the existence of an ongoing cultural resistance to the usual drug treatment and, an arising attention for alternative non-drug procedures. Based on this, our LiSM intervention would be one of these alternatives. However, to adopt our LiSM program the patient must be fit for physical exercises. The studied medicated non-controlled patients referred themselves as being in excellent or good state of health (92%) showing moderate status of physical activity (53%) with 85.1% fully following the WHO’s recommendations for being active individual [14].

In the implementation of effective population-based strategies, diet and physical exercise are the pillars of treatment. Exercise has the most potent effect on endothelium-dependent vasodilatation. The endothelium-derived nitric oxide (eNO) is thought to be necessary to maintain an adequate vascular response to increased blood-flow demands during exercise. For though, shear stress is an important component of exercise that affects vascular NO concentration, and increases the velocity of the endothelial high-affinity/low-capacity transport system for L-arginine [51]. Muscular contraction dependent $[Ca^{++}]$ also modulates eNOS activity but shear stress leads to eNOS phosphorylation on serine residues independent from increases in $[Ca^{++}]$ [52-62].

In our set of experiments, high blood pressure responded to all exercise protocols, irrespective of weight loss. However, the reduction of hypertension by LiSM was followed by increased aerobic conditioning and reduced intake of processed foods along with decreased values of BMI, abdominal fatness, insulin resistance, pro-inflammatory and peroxydative activities [1].

Regarding the hypertension response to the type of exercise, it was demonstrated by the present results, as time-dependent for isolated walking-jogging or strength training and, abbreviated by combining both. Short-period responsiveness could be achieved by either combined (strength-endurance) or hydrogymnastic exercises.

Finally, mostly of the medicated non-controlled patients were from the low-income range (less than US\$ 1,500 a month) and though probably under the Brazilian rules for free of charge medications. Excluding the economical reasons, the two other important points would be their self-perception of being in an excellent/good health status, meaning “I’m feeling good so I’m cured so I don’t need medication anymore” and/or they were younger (60% under 60 yrs) and physically active and (56.8%) able for weekly moderate- activities. In the later instance, the patients probably realized the beneficial effects of being healthy without medicines (and their unpleasant side effects) and looked for the lifestyle modification alternative such as our LiSM program.

On the economic effectiveness side of our LiSM, the Brazilian government spends, in average, US\$ 39.50/month for each diagnosed hypertensive subject [9], US\$ 474



a year ending up to the yearly sum of US \$ 17.3 billion spent with anti-hypertensive medications! Moreover, we found rates of medicated-non controlled hypertensives as 65.2% and 67% for diastolic and systolic BP, respectively. If applied nationwide, these rates would mean a wasting of more than US\$ 14 billion spent with medications that are not working properly! On the other side, the net effectiveness of our 10wk-LiSM in normalizing SBP hypertension was 8.5%. If applied this figure nationwide, we would normalize 3.1 million of hypertensive citizens, at an economic costs of US\$ 1.47 billion! [14], which could be amplified to US\$ 14.2 billion if LiSM is extended to 8mo. and normalizing 31.6% of hypertensive [5]. Thus, exercise training is a time- and type-dependent tool feasible, costless and scientific-based rheostatic-allostatic alternative for the current “sick-care” drug-dependent homeostatic approach to hypertension medicare.

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