

The effects of exercise training on arterial baroreflex sensitivity in neurally mediated syncope patients

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KEYWORDS

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Aims The clinical effects of different modalities of treatment for neurally mediated syncope have been studied for years; however, their influences on its pathophysiological mechanisms still have not been determined. This research aimed to observe the effects of physical training, tilt training, and pharmacological therapy on the arterial baroreflex sensitivity and muscle sympathetic nerve activity in neurally mediated syncope patients.

Methods and results Seventy patients with recurrent neurally mediated syncope were included in this study. Patients were divided into the following four groups, depending on the treatment proposed: (i) physical training, (ii) tilt training, (iii) pharmacological therapy, and (iv) control group. All patients underwent an autonomic evaluation with microneurography, when the vagal and sympathetic arterial baroreflex gain were tested, using graded infusions of phenylephrine or sodium nitroprusside, before and 4 months after the interventions. The vagal and sympathetic arterial baroreflex gain significantly increased after a 4-month protocol of physical training. Tilt training, pharmacological therapy, and the control group had no significant change in the arterial baroreceptor responses.

Conclusion Physical training improves arterial baroreflex sensitivity in neurally mediated syncope patients and could be applied as a non-pharmacological therapeutic alternative for these patients.

Introduction

Pathophysiological mechanisms involved in neurally mediated syncope are not completely understood.^{1,2} Several studies have attempted to identify the pathways involved in this syndrome. Some authors have described a compromised baroreflex regulation in these patients.^{1,2} Alterations in vascular resistance, possibly due to a failure in vessel constriction mediated by muscle sympathetic nerve activity (MSNA) increases, could in part explain this occurrence.^{3,4} On the other hand, it has been reported that neurally mediated syncope patients have an increased MSNA at rest, which could be interpreted as a compensatory mechanism against the deficit in peripheral circulatory control.¹

Although many different proposed treatments are available for neurally mediated syncope, their long-term results are not as good as expected. Studies evaluating the influences of these treatment strategies on the supposed pathophysiological mechanisms are scarce.

Physical training has been described as a useful strategy in the management of this syndrome. The benefits of exercise

in these patients include an increase in blood volume and in leg muscle mass.⁵ These effects improve central blood volume distribution and reduce venous pooling.⁶ Increased orthostatic tolerance was observed in neurally mediated syncope patients who underwent 3 months of physical training.^{7–9} It is also recognized that the arterial baroreflex is closely related to circulatory control during orthostatic stress and during exercise practice in acute or chronic ways.¹⁰ Some authors have described an improvement in baroreflex sensitivity in experimental models involving a physical training programme.^{11–13}

The aim of this study was to evaluate the effects of physical training on vagal and sympathetic arterial baroreflex gain in neurally mediated syncope patients and compare it with other recognized modalities of treatment for this syndrome.

Methods

Study population

Seventy patients were included in this study, which was approved by the Human Subject Protection Committee of the Heart Institute (InCor) and Clinics Hospital of the University of São Paulo Medical School. All subjects gave written informed consent to participate

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in this research. Consecutive outpatients meeting the following inclusion/exclusion criteria were offered participation in the study: (i) age between 15 and 50 years, (ii) neurally mediated syncope diagnosis established by suggestive clinical history and a positive tilt-table test (tilt responses: 38 mixed, 17 cardioinhibitory, and 15 vasodepressive), (iii) both sexes, (iv) recurrent syncope episodes (2 or more episodes within the 6 months before the beginning of the protocol), (v) refractory to general measures like increased salt and water intake, elastic sock wearing, recognition of prodromic symptoms, and fractionated food intake, (vi) absence of any structural heart disease, arrhythmias, diabetes, neurological diseases, and any drug treatment, (vii) absence of regular physical exercise in the last 6 months before the beginning of the protocol, and (viii) no muscle skeletal abnormality (e.g. arthritis) prohibiting participation in an exercise programme. All patients were followed monthly in our ambulatory care centre, where they were asked about their performance in the interventions. The four groups were instructed to optimize the general measures like increased salt and water intake, elastic sock wearing, recognition of prodromic symptoms, and fractionated food intake.

Study protocol

Patients with neurally mediated syncope were divided into the following four groups, according to the modality of treatment proposed: (i) pharmacological therapy (PhT), (ii) physical training (PT), (iii) tilt training (TT), and (iv) control group. The patients of the three intervention groups (PhT, TT, and PT) were divided on the basis of a randomized sequence. Factors like impossibility to come to our rehabilitation centre were considered, in order to include the patient in our study. The control group was designed after the beginning of the study protocol, aiming to create a comparison way among the treatment options and the general measures usually adopted.

Resting MSNA and baroreflex sensitivity were obtained before initiating the therapeutic interventions. The patients, in a fasting state, were positioned for microneurography and a satisfactory nerve-recording site from the peroneal nerve was obtained. Blood pressure (Finapres model 2300, Ohmeda, Englewood, CO, USA) and heart rate (EKG) were measured non-invasively. A venous cannula was inserted into an antecubital vein. Initially, 3 min of resting MSNA, blood pressure, and heart rate were recorded, after a 10 min supine resting period.

The same procedures were repeated 4 months post-interventions.

The initial size of each group were 20 patients in pharmacological therapy group, tilt training group and physical training group, and 10 patients in the control group. We finished our study with 20 patients in the pharmacological therapy group, 14 in the tilt training group, 11 in the physical training group, and nine in the control group.

Muscle sympathetic nerve activity

MSNA was recorded from the right peroneal nerve using the microneurography technique.^{14,15} In brief, the right leg was immobilized and securely positioned on the tilt table using an adjustable leg brace to maximize successful recordings. A unipolar tungsten electrode (uninsulated tip diameter of 1–5 μm , shaft diameter of 200 μm) was inserted into the muscle nerve fascicles of the peroneal nerve for multiunit recordings. Nerve activity signals were amplified by a factor of 50 000–100 000 and band-passed filtered (700–2000 Hz). The signal was then rectified, amplified approximately 100-fold, and integrated (time constant 0.1 s) to obtain a mean voltage display of sympathetic activity. As previously described,¹⁶ we considered a recording of sympathetic nerve activity acceptable: (i) when the microneurography signal demonstrated spontaneous, pulse-coupled bursts of nerve activity that exceeded by three-fold the background noise signal; (ii) when there was no evidence of increased activity over time; (iii) when

activity returned to basal after procedures affecting sympathetic tone. The sympathetic nature of the recordings was indicated by increased activity during hypotensive phase of the Valsalva maneuver or by inhibition of the activity during the blood pressure overshoot of the same maneuver.¹⁶ Muscle sympathetic bursts were identified by visual inspection by a single investigator and were expressed as burst frequency (bursts/min) and bursts/100 heartbeats. The reproducibility of MSNA measured at different time intervals in the same individual expressed as bursts/min is $r = 0.88$, and expressed as bursts/100 heartbeats is $r = 0.91$.¹⁷

Arterial baroreflex sensitivity

After a resting MSNA recording was obtained, baroreflex sensitivity was assessed using a crescent dose infusion of phenylephrine and sodium nitroprusside (25, 50, 100 μg). Infusions were given in ascending order, with each concentration lasting 3 min.

Quantification of arterial baroreflex responses to pharmacological manipulations of blood pressure was achieved by using the regression analysis model, as previously reported,¹⁸ whereby the a values obtained in the regression linear equation ($ax + b$) were assumed to be the variable equivalent to arterial baroreflex sensitivity.

Infusions were given in ascending order, with each concentration lasting 3 min.¹⁶ For our analysis of vagal and sympathetic arterial baroreflex gain, all heart rate and MSNA values obtained minute-to-minute during phenylephrine and sodium nitroprusside infusions were crossed with their respective diastolic arterial pressure values.

Cardiopulmonary exercise testing

All patients underwent cardiopulmonary exercise testing before and 4 months after therapeutic interventions. Maximal exercise capacity was determined by a maximal progressive exercise test on an electromagnetically braked cycle ergometer (Medfit 400L, Medical Fitness Equipment, Maarn, Netherlands), with continuous work rate increments at 60 r.p.m. until exhaustion. Oxygen uptake (VO_2) and carbon dioxide production were determined by gas exchange on a breath-by-breath basis in a computerized system (CAD/Net 2001, Medical Graphics Corporation, St Paul, MN, USA). Peak VO_2 was defined as the maximum attained VO_2 at the end of the exercise period in which the subject could no longer maintain the cycle ergometer velocity at 60 r.p.m. This method is considered the gold standard for assessing exercise capacity.¹⁹ The anaerobic threshold was determined to occur at the break-point between the increase in the carbon dioxide output and VO_2 (V-slope)²⁰ or the point at which the ventilatory equivalent for oxygen and end-tidal oxygen partial pressure curves reached their respective minimum values and began to rise.²¹ When these three parameters for determination of the anaerobic threshold were not coincident, the criterion chosen was the point in which the ventilatory equivalent for oxygen and end-tidal oxygen partial pressure curves reached their respective minimum values and began to rise. Respiratory compensation was determined to occur at the point at which the ventilatory equivalent for carbon dioxide was lowest before a systematic increase and when end-tidal carbon dioxide partial pressure reached a maximum and began to decrease.²² When these two parameters for determination of the respiratory compensation point were not coincident, the criterion chosen was the point in which the ventilatory equivalent for carbon dioxide was lowest before a systematic increase. The reproducibility of the peak VO_2 measured at different time intervals in the same individual expressed as mL/kg/min in our laboratory is $r = 0.95$.

Exercise training programme

The training programme was based on previous studies^{23–25} that demonstrate a conditioning effect. Patients underwent supervised exercise training at the Rehabilitation Unit of the Heart Institute.

The 4-month training programme consisted of three 60 min exercise sessions/week. Each exercise session consisted of 5 min stretching exercises, 40 min of cycling on an ergometer bicycle, 10 min of local strengthening exercises (sit-ups, push-ups and pull-ups), 5 min of cool down with stretching exercises. The exercise intensity was established by heart rate levels that corresponded to an anaerobic threshold up to 10% below the respiratory compensation point obtained in the cardiopulmonary exercise test. When a training effect was observed, as indicated by a decrease of 8–10% in heart rate during exercise, the bicycle work rate was increased by 0.25 or 0.5 k.p.m. to return to target heart rate levels. In case of any symptom, the training session was interrupted, and the patient assumed a supine position.

Tilt training programme

The tilt training programme was performed at home. An exception was made for the first week when the subjects performed the tilt training sessions at the hospital, under supervision and accompanied by one family member. Subjects were instructed to maintain an upright posture for 30 min, if tolerated, in a three times/week programme, standing and leaning with the upper back against a wall, the feet 15 cm away from the wall. These home sessions should be performed in a safe environment, under the supervision of a family member. Sessions should be interrupted at the first symptom occurrence, when the patient was instructed to assume the supine position. All patients were instructed to keep a diary, describing the training sessions (exposure duration and the stopping reason, if <30 min). Weekly phone calls were performed to each patient, in order to maintain the protocol compliance in this group.

Pharmacological therapy

In the pharmacological therapy group, the drugs used were fludrocortisone (1–2 mg/kg/day), beta-blockers (1–2 mg/kg/day), or serotonin reuptake inhibitors (sertraline—50 mg/day or fluoxetine—20 mg/day).

The drug was chosen empirically and maintained according to the tilt-table test response; modifications of dosage or type of drug were made when a positive response to tilt was achieved after therapy introduction.²⁶

Control group

The control group was instructed to optimize the general measures and to avoid the triggers, as previously described. Any symptom observed was to be reported to researchers. Participants were also to avoid any regular exercise programme.

Statistical analysis

The data are presented as mean \pm SD. One-way ANOVA was performed to compare the resting characteristics of the patients. Scheffe's *post hoc* comparison was used to determine differences between groups, if necessary. To determine the differences between slopes in arterial baroreflex sensitivity, two-way ANOVA was performed to compare the values in the four groups. In case of significance, Scheffe's *post hoc* comparison was used to determine differences between groups. A *P*-value of <0.05 was considered statistically significant.

Results

Baseline measurements

The clinical characteristics of the patients are shown in *Table 1*. There were no significant differences in age, weight, height, sex, heart rate, peak oxygen uptake, MSNA (bursts/min), and MSNA (bursts/100 heartbeats). We were able to achieve good MSNA recordings in 54 patients in our study. The other patients were not included in the statistical analysis.

Clinical recurrence

All patients included in this study presented at least two or more episodes within the 6 months before the beginning of the protocol. Our clinical follow-up was taken during the time of each intervention (4 months). The pharmacological treatment group presented four syncope episodes in four different patients (one each). Absence of syncope episodes was verified in the tilt training group. Two syncope episodes were observed in the control group, in two different patients, and two syncope episodes were observed in two different patients, in the physical training group.

Muscle sympathetic nerve activity pre- and post-interventions

Resting MSNA measures were not different in the four groups. Nevertheless, a variation was observed in the control group, as presented in *Table 2*. MSNA, evaluated in bursts/100 heartbeats showed a significant increase in the post-intervention period (17 ± 11 vs. 30 ± 7 , $P = 0.00$).

Table 1 Baseline physiologic parameters

	CO group (n = 9)	PT group (n = 11)	TT group (n = 14)	PhT (n = 20)	P-value
Age (years)	27 \pm 3	26 \pm 3	21 \pm 2	26 \pm 2	0.46
Gender (M/F)	4/5	6/5	4/11	8/12	0.53
Weight (kg)	65 \pm 5	68 \pm 4	57 \pm 3	62 \pm 3	0.24
Height (m)	1.68 \pm 0.6	1.69 \pm 0.5	1.65 \pm 0.7	1.68 \pm 0.6	0.58
Peak VO ₂ (mL/kg/min)	30 \pm 10 (79%)	27 \pm 8 (72%)	25 \pm 6 (63%)	25 \pm 6 (65%)	0.25
(% predicted normal value)					
MAP (mmHg)	97 \pm 8	99 \pm 12	102 \pm 13	98 \pm 7	0.69
HR (b.p.m.)	68 \pm 15	69 \pm 9	69 \pm 14	69 \pm 11	0.98
MSNA (bursts/min)	11 \pm 7	20 \pm 8	17 \pm 9	18 \pm 9	0.17
MSNA (bursts/100 heartbeats)	17 \pm 11	36 \pm 12	25 \pm 13	25 \pm 9	0.15

Values are mean \pm SD.

CO group, control group; PT group, physical training group; TT group, tilt training group; PhT group, pharmacological therapy group; VO₂, oxygen uptake; MAP, mean arterial pressure; HR, heart rate; MSNA, muscle sympathetic nerve activity.

Table 2 Cardiopulmonary and haemodynamic characteristics of all groups pre- and post-interventions (4 months)

	Groups	Pre-interventions	Post-interventions	P-value
Peak VO ₂ (mL/kg/min)	Control	30 ± 10	28 ± 9	0.54
	Physical training	27 ± 8	33 ± 9 ^{a,b}	0.04 ^a ; 0.05 ^b
	Tilt training	25 ± 6	25 ± 9	0.89
	Drug therapy	25 ± 6	24 ± 6	0.74
MAP (mmHg)	Control	97 ± 8	97 ± 10	0.91
	Physical training	99 ± 12	96 ± 9	0.65
	Tilt training	102 ± 13	100 ± 8	0.56
	Drug therapy	98 ± 7	101 ± 12	0.23
HR (b.p.m.)	Control	68 ± 15	61 ± 17	0.06
	Physical training	69 ± 9	60 ± 8 ^a	0.01
	Tilt training	69 ± 14	71 ± 12	0.56
	Drug therapy	69 ± 11	64 ± 8 ^a	0.00
MSNA (bursts/min)	Control	11 ± 7	13 ± 9	0.63
	Physical training	20 ± 8	19 ± 10	0.42
	Tilt training	17 ± 9	18 ± 9	0.89
	Drug therapy	18 ± 9	18 ± 10	0.87
MSNA (bursts/100 heartbeats)	Control	17 ± 11	30 ± 7 ^a	0.00
	Physical training	36 ± 12	29 ± 14	0.13
	Tilt training	25 ± 13	28 ± 11	0.23
	Drug therapy	25 ± 9	27 ± 10	0.22

Values are mean ± SD.

VO₂, oxygen uptake; MAP, mean arterial pressure; HR, heart rate; MSNA, muscle sympathetic nerve activity.

^aVs. pre-interventions.

^bVs. other groups (ANOVA).

Heart rate pre- and post-interventions

The physical training group had a significant decrease in the baseline heart rate (69 ± 9 vs. 60 ± 8 b.p.m., $P = 0.01$), as did the pharmacological therapy group (69 ± 11 vs. 64 ± 8 b.p.m., $P = 0.006$). The control group and the tilt training group did not have significant differences. Values are fully presented in *Table 2*.

Peak oxygen uptake pre- and post-interventions

Patients who underwent physical training had a marked increase in peak oxygen uptake, compared with the other groups (27 ± 8 vs. 33 ± 9 mL/kg/min, $P = 0.04$). Data are fully presented in *Table 2*.

Vagal and sympathetic arterial baroreflex sensitivity

MSNA demonstrated a better response after both infusions in the physical training group, as shown in *Figure 1* ($P = 0.04$). The patients in the control group, when receiving tilt training and pharmacological therapy, did not have any significant changes, as observed in *Figure 1A–D*.

On the basis of vagal and sympathetic arterial baroreflex gain, heart rate demonstrated a better response after both infusions, in the physical training group, as shown in *Figure 2* ($P = 0.03$). Similar to the MSNA response, the control group, tilt training, and pharmacological therapy group did not have any significant changes, as shown in *Figure 2A–D*.

Discussion

One of the initial observations of our study is that resting MSNA values showed important variations among the

patients and were not different from the profile previously observed in the control subjects in our laboratory.^{23,27} This finding opposes the findings of other authors¹ who described an increased resting MSNA in neurally mediated patients, suggesting a great heterogeneity of autonomic tone among them.

The variation in the MSNA observed in our control group, not undergoing any specific intervention, suggests that different patterns of autonomic tone may occur not only among patients, but also in the same patient over time. This fact could explain the long periods of symptoms remission observed in these patients; it could also justify the difficulties in determining one single pathophysiological mechanism and achieving an appropriate treatment for this syndrome.

Until now, the impact of different therapeutic interventions proposed for the mechanisms responsible for the circulatory control in neurally mediated syncope patients is not well established. Altered autonomic circulatory control, especially in high- (arterial) and low- (cardiopulmonary) pressure receptors is apparently involved in neurally mediated syncope episodes, according to the literature. Wijeyesundera *et al.*² demonstrated an attenuated baroreflex mediated by cardiopulmonary receptors in presyncopal subjects who fainted during the tilt table test. This finding could signify a lower ability to increase the sympathetic tone aiming to obtain a vasoconstrictor response on skeletal muscle, which is desired once the subject is exposed to orthostasis. Mosqueda-Garcia *et al.* in 1997¹⁶ also described the inability to increase MSNA during orthostatic stress in neurally mediated syncope patients. To reinforce this hypothesis, Furlan *et al.* in 1998²⁸ observed lower MSNA, followed by an overreacted heart rate response, suggesting a deranged sympathetic outflow to the vessels but not to

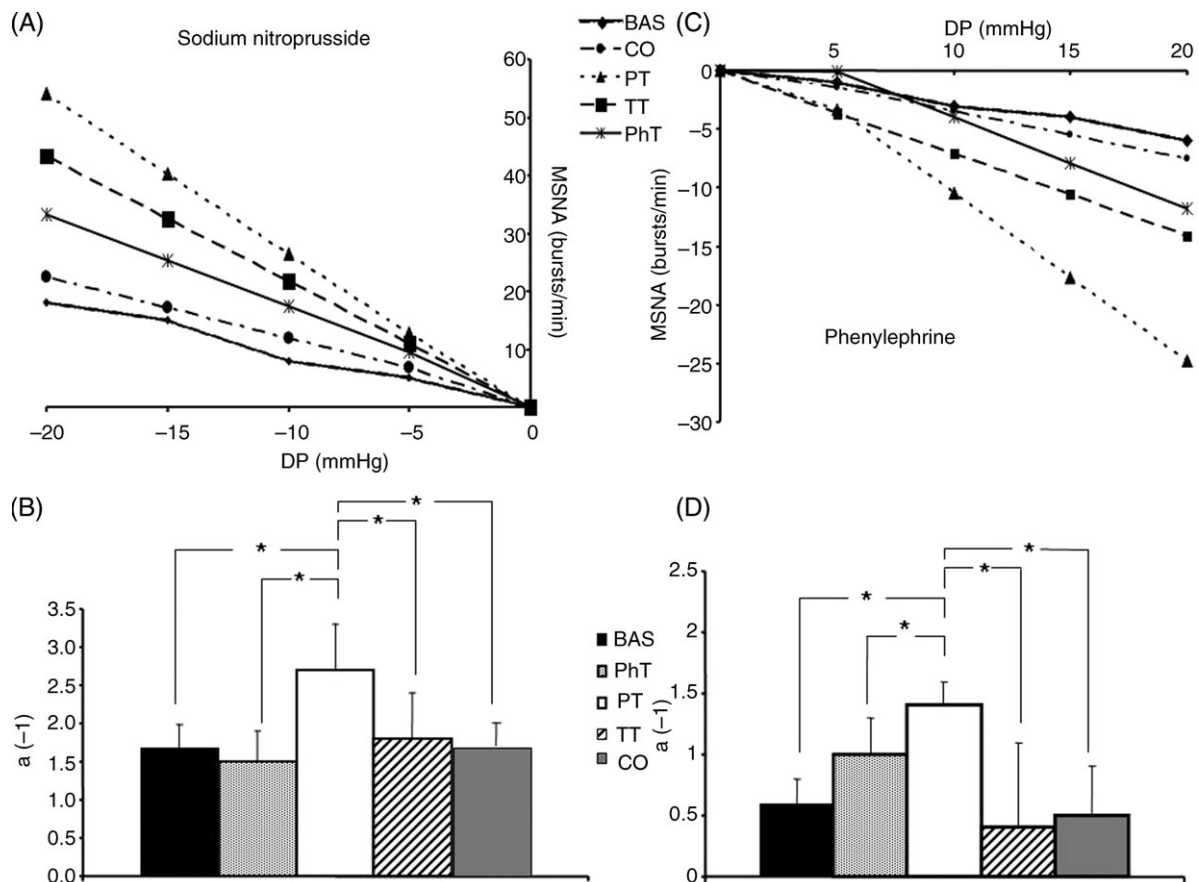


Figure 1 Arterial baroreflex sensitivity for MSNA in the four groups during sodium nitroprusside infusions (A) and phenylephrine infusions (C). Note that the physical training group was the only one that showed improvement in the a values, which are related with the arterial baroreflex sensitivity for MSNA, as demonstrated in items B and D. * $P = 0.04$ vs. other groups; BAS, mean of the baseline values in the four groups; CO, control group; PT, physical training group; TT, tilt training group; PhT, pharmacological therapy group; MSNA, muscle sympathetic nerve activity; DP, diastolic pressure; a , arterial baroreflex sensitivity.

the heart, in the chronic orthostatic intolerance. Morillo *et al.*²⁹ demonstrated that neurally mediated syncope patients were unable to maintain the MSNA and consequently, the vasoconstriction in the lower limbs, when undergoing long periods of standing. In addition to these data, Béchir *et al.*¹ described increased resting MSNA in syncopal patients, compared with that in a control group, suggesting a dysfunction in autonomic balance, which participates in the pathophysiology of neurally mediated syncope. In review, poor blood volume distribution, characterized by a severe venous pooling instead of maintenance of the central blood flow, is one of the most important causes of vasovagal reactions.

Concerning exercise training, although frequently recommended, the literature reporting its effects on neurally mediated syncope patients is rare. To our knowledge, no other published studies compare the effects of exercise training to any other kind of currently applied treatment on the supposed pathophysiological mechanisms.

The benefits of exercise on arterial baroreflex sensitivity are well established in experimental models.^{11–13,30} In our study, to evaluate arterial baroreflex sensitivity, we have chosen the crescent dose infusion method, with the patient in a supine position,¹⁶ trying to avoid any exacerbation reaction of the circulatory system during sodium nitroprusside infusion. We believe that by using this method, we can maintain better control over blood pressure than performing bolus infusions, considering that these

patients have impaired baroreflex sensitivity, as demonstrated by several authors.^{2,16,29}

Our hypothesis was that a regular exercise programme would promote systemic modifications potentially beneficial to vasovagal syncope patients. It is well described that chronic aerobic exercise can increase blood volume and muscle tone, contributing to optimization of venous return, a desirable effect to neurally mediated syncope patients. In fact, Wieling and van Lieshout³¹ described an increase in orthostatic tolerance and plasma volume in subjects who participate in a moderate physical training program. The benefits of exercise in improving orthostatic tolerance were demonstrated by Allen *et al.*,³² when 2 identical twins with a history of fainting were studied. One participated in a physical exercise program, while the other remained sedentary. After 3 weeks, both twins underwent a head-up tilt, and only the trained twin tolerated the test. Physical training can also induce modifications in the autonomic nervous system, which can oppose those observed in vasovagal syncope patients. Our results demonstrated, for the first time, the effects of a physical training program on arterial baroreflex sensitivity, as well as that there are no effects from other available therapeutic interventions. No significant modification was observed during a 4-month follow-up after tilt training, drug therapy, and general measures; however, in the physical training group, positive and significant modulation of vagal and sympathetic

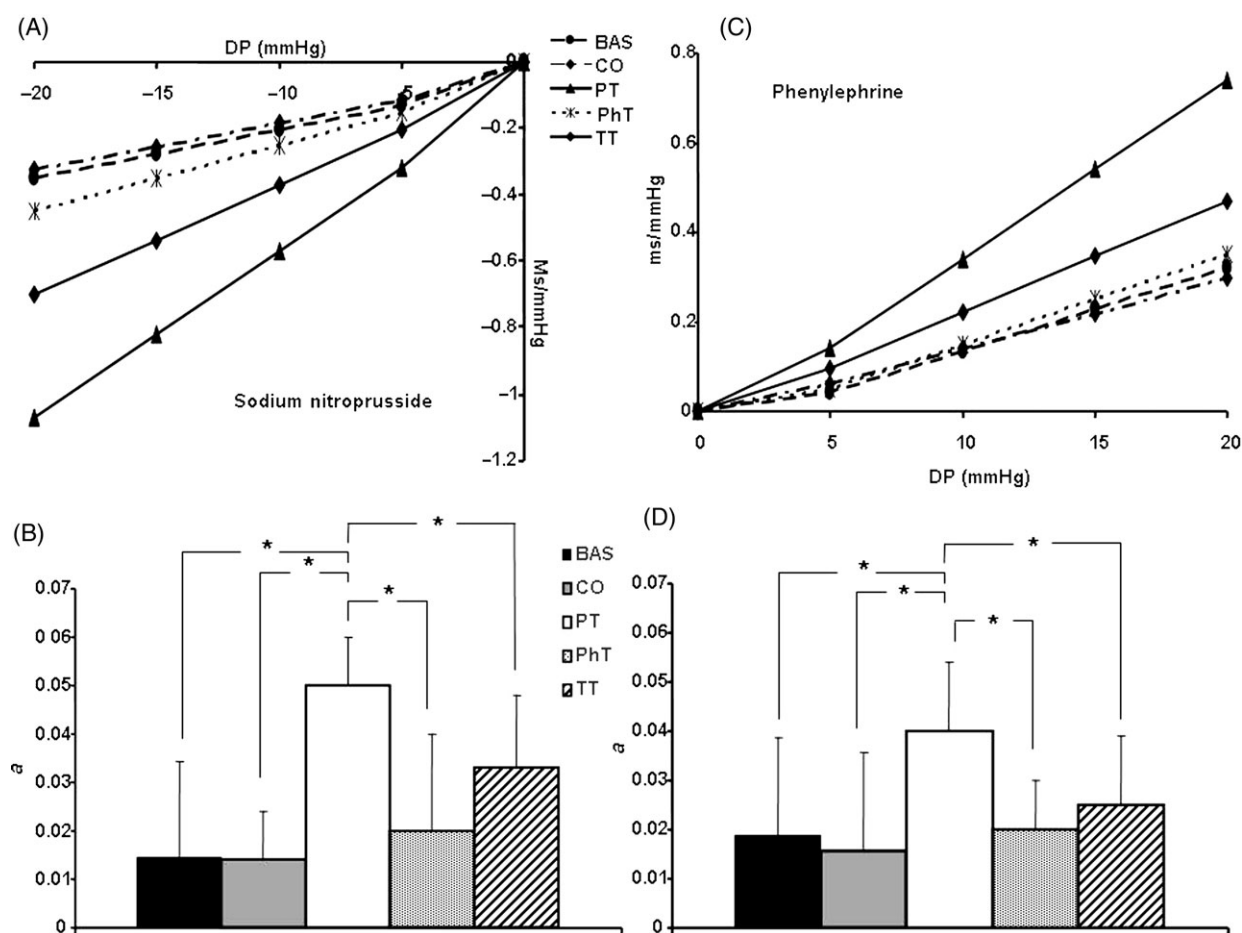


Figure 2 Arterial baroreflex sensitivity for heart rate in the four groups during sodium nitroprusside infusions (A) and phenylephrine infusions (C). Note that the physical training group was the only one that showed improvement in the α values, which are related with the arterial baroreflex sensitivity for heart rate, as demonstrated in items B and D. * $P = 0.03$ vs. other groups; BAS, mean of the baseline values in the four groups; CO, control group; PT, physical training group; TT, tilt training group; PhT, pharmacological therapy group; DP, diastolic pressure, α , arterial baroreflex sensitivity.

arterial baroreflex gain was achieved. In this syndrome, an improvement in arterial baroreflex sensitivity is desirable, once MSNA increases during an arterial pressure fall, as observed during orthostatic stress, and could diminish the venous pooling and create better blood redistribution.

The effectiveness of exercise training conditioning in our patients was observed by the increased oxygen uptake, not achieved in the other groups. A lower resting heart rate was obtained in the training group, after the follow-up period. This effect was also observed in the pharmacological group, probably due to beta-blockers and other drugs like fludrocortisone, which can interfere with plasma volume, venous return, and directly with arterial pressure, although these drugs did not promote any change in arterial baroreflex sensitivity.

Several authors have described the tilt training efficacy in increasing orthostatic tolerance in neurally mediated syncope patients.^{33,34} Our study demonstrated that a tilt training programme does not affect arterial baroreflex sensitivity. The possible reconditioning effects of tilt training on circulatory reflex control may especially affect the cardiopulmonary reflexes, which were not evaluated in this study.

The present study had some limitations. One of the major drawbacks of our study is related with the fact that we did not perform a randomized controlled trial. Our patients were included in each treatment group considering factors like the impossibility to come to our rehabilitation centre,

for example. The control group was introduced during our study protocol, what may cause some interference in the obtained results. Future studies must be taken in order to eradicate this bias. Other important factor is related with the tilt training performed at home. Despite the fact that weekly phone calls were performed to each patient in the tilt training group, added to the obligation of fulfill a diary with information like tilt tolerance and symptoms when the patient were not able to complete the 30 min required in the tilt training session, we admit that some patients could not describe the absolutely true in their reports. A larger follow-up period should also be considered, in order to verify the clinical effects of each treatment in neurally mediated syncope patients.

In conclusion, physical training improved vagal and sympathetic arterial baroreflex gain, in neurally mediated syncope patients, whereas the other treatments did not achieve the same results. This fact can justify the current prescription of exercise in the management of neurally mediated syncope.

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Conflict of interest: none declared.

References

- Béchar M, Binggeli C, Corti R, Chenevard R, Spieker L, Ruschitzka F, Lüscher TF, Noll G. Dysfunctional baroreflex regulation of sympathetic nervous activity in patients with vasovagal syncope. *Circulation* 2003; **107**:1620–1625.
- Wijesundera DN, Butler GC, And S, Pollard MJ, Picton P, Floras JS. Attenuated cardiac baroreflex in men with presyncope evoked by lower body negative pressure. *Clin Sci* 2001; **100**:303–309.
- Thomson HL, Lele SS, Atherton JJ, Wright KN, Stafford W, Frenneaux MP. Abnormal forearm responses during leg exercise in patients with vasovagal syncope. *Circulation* 1995; **92**:2204–2209.
- Gulli G, Cooper VL, Claydon VE, Hainsworth R. Prolonged latency in the baroreflex mediated vascular response in subjects with postural related syncope. *Clin Auton Res* 2005; **15**:207–212.
- Convertino VA, Montgomery LD, Greenleaf JE. Cardiovascular responses during orthostasis: effect of an increase in $\dot{V}O_{2\max}$. *Aviat Space Environ Med* 1984; **55**:702–708.
- Mayerson HS, Burch GE. Relationships of tissue (subcutaneous and in transmuscular) and venous pressures to syncope induced in man by gravity. *Am J Physiol* 1940; **128**:258–269.
- Mtinangi BL, Hainsworth R. Increased orthostatic tolerance following moderate exercise training in patients with unexplained syncope. *Heart* 1998; **80**:596–600.
- Mtinangi BL, Hainsworth R. Effect of moderate exercise training on plasma volume, baroreceptor sensitivity and orthostatic tolerance in healthy subjects. *Exp Physiol* 1999; **84**:121–130.
- Carroll JF, Wood CE, Pollock MI, Graves JE, Convertino VA, Lowenthal DT. Hormonal responses in elders experiencing pre-syncope symptoms during head-up tilt before and after exercise training. *J Gerontol A Biol Sci Med Sci* 1995; **50**:M324–M329.
- Krieger EM, Brum PC, Negrão CE. Role of arterial function on cardiovascular adjustments to acute and chronic dynamic exercise. *Biol Res* 1998; **31**:273–279.
- Brum PC, da Silva GJJ, Moreira ED, Ida F, Negrão CE, Krieger EM. Exercise training increases baroreceptor gain activity in normal and hypertensive rats. *Hypertension* 2000; **36**:1018–1022.
- Silva GJJ, Brum PC, Negrão CE, Krieger EM. Acute and chronic effects on baroreflexes in spontaneously hypertensive rats. *Hypertension* 1997; **30**:714–719.
- Liu JL, Irvine S, Reid IA, Patel KP, Zucker IH. Chronic exercise reduces sympathetic nerve activity in rabbits with pacing-induced heart failure. *Circulation* 2000; **102**:1854–1862.
- Delius W, Hagbarth KE, Hongell A, Wallin BG. Maneuvers affecting sympathetic outflow in human muscle nerves. *Acta Physiol Scand* 1972; **84**:82–94.
- Valbo AB, Hagbarth KE, Torebjörk HE, Wallin BG. Somatosensory, proprioceptive and sympathetic activity in human peripheral nerves. *Physiol Rev* 1979; **59**:919–957.
- Mosqueda-Garcia R, Furlan R, Fernandez-Violante R, Desai T, Snell M, Jarai Z, Ananthram V, Robertson RM, Robertson D. Sympathetic and baroreflex function in neurally mediated syncope evoked by tilt. *J Clin Invest* 1997; **99**:2735–2744.
- Fagius J, Wallin BG. Long-term variability and reproducibility of human muscle nerve activity at rest, as reassessed after a decade. *Clin Auton Res* 1993; **3**:201–205.
- Smyth HS, Sleight P, Pickering GW. Reflex regulation of arterial pressure during sleep in man. A quantitative method of assessing baroreflex sensitivity. *Circ Res* 1969; **24**:109–121.
- Cohen-Solal A. Cardiopulmonary exercise testing in chronic heart failure. In: Wasserman K, ed. *Exercise Gas Exchange in Heart Disease*. 1st ed. Armonk, NY: Futura Publishing Company; 1996. p17–38.
- Beaver WL, Wasserman K, Whipp BJ. A new method for detecting the anaerobic threshold by gas exchange. *J Appl Physiol* 1986; **60**:2020–2027.
- Wasserman K, Whipp BJ, Koyal SN, Beaver WL. Anaerobic threshold and respiratory gas exchange during exercise. *J Appl Physiol* 1973; **33**:236–243.
- Wasserman K, Hansen JE, Sue DY. Principles of exercise testing and interpretation. In: Wasserman K, Hansen JE, Sue DY, Whipp BJ, ed. *Measurements of the Physiological Response to Exercise*. Philadelphia, PA: Lea & Febiger; 1987. p27–46.
- Roveda F, Middlekauff HR, Rondon MUPB, Reis SF, Souza M, Nastari L, Barreto ACP, Krieger EM, Negrão CE. The effects of exercise training on sympathetic neural activation in advanced heart failure. *JACC* 2003; **42**:854–860.
- Keteyan SJ, Levine AB, Brawner CA, Kataoka T, Rogers FJ, Schairer JR, Stein PD, Levine TB, Goldstein S. Exercise training in patients with heart failure: a randomized controlled trial. *Ann Intern Med* 1996; **124**:1051–1057.
- Kilavouri K, Toivonen L, Naveri H, Leinonen H. Reversal of autonomic derangement's by physical training in chronic heart failure assessed by heart rate variability. *Eur Heart J* 1995; **16**:490–505.
- Hachul D, Scanavacca M, Sosa E. Does a role exist for tilting-guided therapy in the management of neurocardiogenic syncope? *Arq Bras Cardiol* 2002; **78**:167–171.
- Kuniyoshi FHS, Trombetta IC, Batalha LT, Rondon MUPB, Laterza MC, Gowdak MMG, Barreto ACP, Halpern A, Vilares SMF, Lima EG, Negrão CE. Abnormal neurovascular control during sympathoexcitation in obesity. *Obes Res* 2003; **11**:1411–1419.
- Furlan R, Jacob G, Snell M, Robertson D, Porta A, Harris P, Mosqueda-Garcia R. Chronic orthostatic intolerance: a disorder with discordant cardiac and vascular sympathetic control. *Circulation* 1998; **98**:2154–2159.
- Morillo CA, Eckberg DL, Ellenbogen LA, Beightol LA, Hoag JB, Tahvanainen KUO, Kuusela TA, Diedrich AM. Vagal and sympathetic mechanisms in patients with orthostatic vasovagal syncope. *Circulation* 1997; **96**:2509–2513.
- De Angelis K, Wichi RB, Jesus WRA, Moreira E, Morris M, Krieger EM, Irigoyen MC. Exercise training changes autonomic cardiovascular balance in mice. *J Appl Physiol* 2004; **96**:2174–2178.
- Wieling W, van Lieshout JJ. The fainting risk. *Clin Auton Res* 2002; **12**:242–249.
- van Lieshout JJ. Exercise training and orthostatic intolerance: a paradox? *J Physiol* 2003; **551**:401. Published online ahead of print July 1, 2003.
- Numata T, Abe H, Nagatomo T, Sonoda S, Kohshi K, Nakashima Y. Successful treatment of malignant neurocardiogenic syncope with repeated tilt training program. *Jpn Circ J* 2000; **64**:406–409.
- Reybrouck T, Heidebüchel H, Van De Werf F, Ector H. Tilt training: a treatment for malignant and recurrent neurocardiogenic syncope. *PACE* 2000; **23**:493–498.