



## Cardiovascular responses to isometric handgrip exercise in young patients with recurrent vasovagal syncope

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### ABSTRACT

**Objective:** Arterial blood pressure (BP) increased in healthy humans in response to isometric handgrip (IHG), but the pattern of the relative contribution of cardiac output (CO) and total peripheral resistance (TPR) changes to the pressor response is different among individuals. We investigated whether patients with recurrent vasovagal syncope (VVS) have a similar pattern of individual CO, TPR and pressor responses to IHG, as healthy subjects. **Methods:** 32 patients ( $27.5 \pm 2.6$  years), and 30 age-matched controls. Autonomic function was evaluated using finger-photoplethysmography to measure BP and heart rate (HR) response to gravitational stress ( $\Delta$ BP,  $\Delta$ HR), Valsalva maneuver (VM) and baroreflex sensitivity (BRS), and BP HR and CO changes during IHG. **Results:**  $\Delta$ BP,  $\Delta$ HR, VM and IHG tests did not show significant difference between VVS patients and controls, although BRS was lower in VVS group ( $p < 0.05$ ). Pattern of individual pressor, CO and TPR responses to IHG was significantly different between VVS patients and healthy subjects (Chi square,  $p = 0.0246$ ). In 100% of the healthy subjects BP increased during IHG, but in a 19% of the patients BP (CO and TPR) did not increase during IHG. In VVS patients, the autonomic tests ( $\Delta$ BP,  $\Delta$ HR, VM and BRS) showed no significant differences between the group with BP increase and the group without pressor response. **Conclusion:** In VVS patients, the pattern of individual CO and TPR changes to IHG is different from healthy subjects. VVS patients may present an abnormal regulation of cardiovascular responses to IHG, with preserved cardiovagal and cardiac sympathetic function.

### 1. Introduction

The hemodynamic manifestation of the Vasovagal Syndrome (VVS), a common condition in medical practice, is characterized by a reduction in cerebral blood flow due to an abrupt hypotension accompanied by bradycardia (Mosqueda-García et al., 2000). VVS is characterized by a transient instability of the neuro-cardiovascular reflexes, but the theoretical explanations of such instability are still debated. The hypotension occurring during the VVS episode was initially explained by an acute vasodilatation, but further studies showed that cardiac output (CO) fell before the syncope, thus a decreasing CO could be the principal mechanism of hypotension (Jardine et al., 2017).

VVS is an intermittent condition, thus during the syncope free period, usually patients have normal sympathetic and vagal responses to Valsalva maneuver and normal vagal modulation of heart rate during deep breathing. There is some evidence of subtle autonomic dysfunction in groups of VVS patients during basal conditions: 1) abnormal cardiac autonomic modulation (Zygmunt and Stanczyk, 2004, Longin

et al., 2008, Shinohara et al., 2014), 2) low supine systolic arterial blood pressure (BP) due to abnormal norepinephrine spillover with low tyrosine hydroxylase levels (Vaddadi et al., 2011) and 3) neurohumoral dysfunction with different purinergic profiles (Guieu et al., 2015).

During isometric exercise, a contraction of a small mass of muscle causes sympathetic activation, which increases BP and heart rate (HR). The sympathetic activation involves a peripheral afferent component (input from exercising skeletal muscle receptors: mechanoreflex and metaboreflex), and a central component (brain centers integration), and can be modulated by arterial baroreceptors and chemoreceptors systems (Fisher et al., 2015). The handgrip using a static low-intensity voluntary muscle contraction (e.g. 30% of maximal contraction) is a reliable physiological test for studying cardiovascular responses to the transient sympathoexcitatory stress. In healthy subjects, the changes in CO and total peripheral resistance (TPR) mediating the pressor response during to isometric handgrip exercise (IHG) showed a pattern of individual differences. Thus, subjects showing greater increase in CO had smaller increase in TPR and vice versa, hence a group of subjects

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**Table 1**  
Demographic characteristics of health subjects and VVS patients.

	Healthy subjects	VVS patients
<i>n</i>	30	32
Sex	10 male/20 female	5 male/27 female
Age (years)	31.2 ± 1.9	28.8 ± 2.3
Weight (kg)	66.5 ± 1.9	59.7 ± 1.8*
Height (cm)	166.0 ± 1.6	163.2 ± 1.6
BMI (kg/m <sup>2</sup> )	24.1 ± 0.6	22.4 ± 0.6*
Valsalva ratio	1.8 ± 0.1	1.7 ± 0.1
BRS (ms/mm Hg)	11.0 ± 0.5	8.4 ± 0.7*
MAP (mm Hg)	68.0 ± 2.1	74.6 ± 2.9
Ps (mm Hg)	101.8 ± 2.7	110.6 ± 2.6*
Pd (mm Hg)	51.4 ± 1.9	56.4 ± 2.4
CO (L/min)	5.3 ± 0.2	5.7 ± 0.2
HR (beat/min)	66.7 ± 1.8	76.7 ± 2.5*
TPR (mm Hg min/L)	13.6 ± 0.8	13.8 ± 0.8

Mean ± SEM; Mean ± SEM. BMI = body mass index, BRS = baroreflex sensitivity, MAP = mean arterial blood pressure, SBP = systolic arterial blood pressure, DBP = diastolic arterial blood pressure, CO = cardiac output, HR = heart rate, TPR = total peripheral resistance. Mean ± SEM: \**p* < 0.05 Student unpaired test, VVS patients vs. healthy subjects.

increased CO, others increased TPR and others increased CO & TPR (Watanabe et al., 2014). The pattern of individual differences in the components of the pressor response, depends on variations in arterial baroreflex function, influence of central command and possibly in differences in muscle metaboreflex sympathetic activation (Watanabe et al., 2014).

Studies of IHG pressor responses in VVS patients, using intermittent arm cuff inflation (Khurana and Setty, 1996) and studies with beat-to-beat photoplethysmography (Van den Berg and Smit, 1997, Jardine et al., 2009) had shown diverse BP and HR changes, including a group of patients with decreased pressor response. There are no studies that assess the pattern of individual CO and TPR behavior during IHG in VVS patients. In the present study we hypothesized that in VVS patients the individual pattern of pressor, CO and TPR responses during isometric exercise would be different from healthy subjects.

## 2. Methods

### 2.1. Subjects and ethical approval

The study was performed in 32 patients with recurrent VVS and 30 age-matched healthy subjects. The diagnosis of VVS was based upon clinical criteria according to a Consensus Statement (Sheldon et al., 2015). All patients had typical VVS with an identify trigger factor and presence of prodromal symptoms. Recurrent VVS was defined as two or more episodes of syncope during the last 12 months. All patients had normal physical examination and normal cardiac evaluation. The exclusion criteria were: epilepsy, heart failure, orthostatic hypotension, central or peripheral nervous system disease, and drugs treatment that could interfere with autonomic nervous system function. Healthy subjects were recruited from medical students, hospital personal and their relatives. The inclusion criteria were: normal arterial blood pressure, normal physical fitness, nonsmokers and non-heavy alcohol drinker and nonuse of illicit drugs. The subjects gave an informed consent. The protocol of the study was approved by Ethical Committee of the School of Medicine. Pontificia Universidad Católica de Chile.

### 2.2. Study protocol

The study was conducted in a quiet room with the temperature at 23–25 °C. Subjects were asked to abstain from coffee and alcohol intake for at least 24 h. Before the examination the subjects were taught about how to perform each procedure. The experience of handgrip using the dynamometer, with a maximal voluntary contraction and with a 30%

was trained.

All tests were done in the morning at least 2 h after a light breakfast. Autonomic function was evaluated using a finger photoplethysmography Finometer™ device (Finapres Medical Systems B.V., Netherlands), the monitored cuff was placed around the middle finger with the cuff aligned at level of the heart: gravitational stress: arterial blood pressure (BP) and heart rate (HR) change on active standing ( $\Delta$ BP,  $\Delta$ HR), Phases I, II, III and IV and Valsalva ratio, Baroreflex sensitivity (BRS). For isometric handgrip test (IHG), the subjects were in supine position, and were asking to perform the handgrip (initially at maximal voluntary handgrip contraction and then at 30% of maximal contraction during 3 min, using a handgrip dynamometer (Vigometer, KLS Martin Group, Germany) held in the right hand. Measurements: basal BP and HR were recorded before and during the 3 min of IHG, beat-to-beat BP and HR changes were monitored. The procedure was repeated in those patients without BP change during the IHG. CO was measured with the finger photoplethysmography Finometer (Bogert et al., 2010) and total peripheral resistance (TPR) was calculated as the quotient between mean arterial blood pressure (MAP) and CO.

### 2.3. Statistical

Data was expressed as mean ± SEM. The criterion for classifying BP, CO and TRP as unresponsive to IHG, was that the values of the individual responses were within 95% of the confidence interval of the mean baseline values. The comparison of 2 groups was performed with the Student *t*-test. One-way ANOVA followed by Dunnett multiple test was used for multiple comparisons. Differences of individual components were assessed with Chi squared test.

## 3. Results

### 3.1. Demographic characteristics of healthy subjects and VVS patients are shown in Table 1

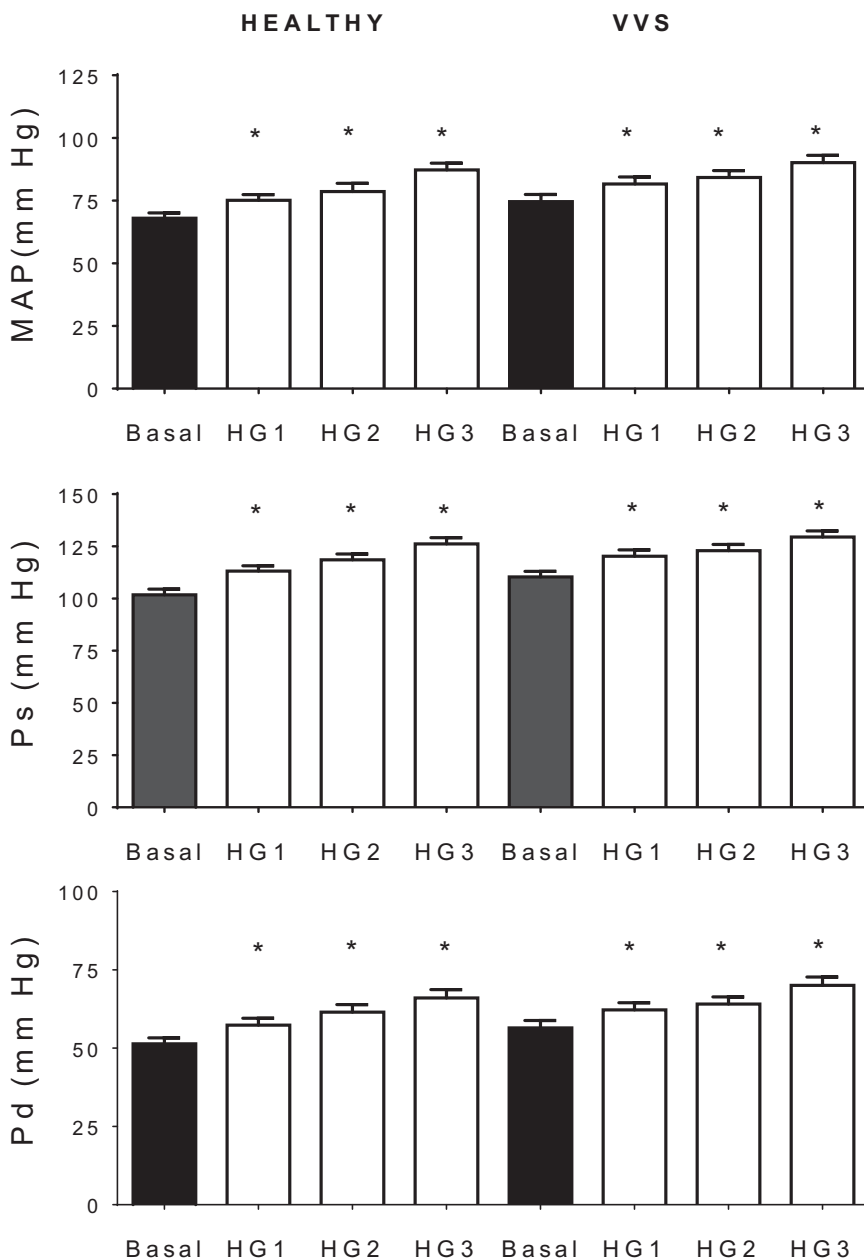
Female were 66.7% in healthy subject and 87.5% in VVS patients. Mean age of beginning of syncope was 15 ± 4.1 (range 9–25) years. All VVS patients had recurrent syncope: mean 2.3 (range 2–4) episodes during the preceding 12 months. Prodromal symptoms were reported in all VVS patients. Triggers factors were: postural in 100%, emotional induced in 33%, warm environment in 21%. None of the patients reported syncope during sleeping. Mean age was not different between both groups. Weight (kg) and BMI were higher in healthy subjects. BRS (ms/mm Hg) index was significant low in VVS patients (*p* < 0.05). Basal mean systolic BP and HR were significantly higher in VVS patients (*p* < 0.05).

### 3.2. Cardiovascular responses to IHG

The mean average responses of the overall sample showed that in both healthy subjects and patients groups the systolic BP, diastolic BP and HR increased significantly during IHG (*p* < 0.05). Mean arterial blood pressure (MAP) and CO increased significantly during IHG in both groups (*p* < 0.05) (Figs. 1 and 2).

#### 3.2.1. Analysis of individual components of the pressor responses during IHG

The pattern of the contribution of CO and TPR between VVS patients versus healthy subjects was respectively: CO increases in 45.7% vs 53.6%, TPR increased in 31% vs. 23.3%, both CO and TPR increased 6.5% vs 23.3%, and no increase of CO and TPR without BP rise was observed in 19% of VVS patients, but not in healthy subjects. The individual distribution of CO and TPR changes were significantly different between VVS patients and healthy subjects (Chi square, *p* = 0.0246), see Table 2.



**Fig. 1.** Mean pressor response to handgrip. Mean ± SEM. MAP = mean arterial blood pressure, SBP = systolic arterial blood pressure, DBP = diastolic arterial blood pressure. Basal = baseline values; HG1–3, values obtained at 1–2 and 3 min of handgrip (HG). \**p* < 0.05. One-way ANOVA followed by Dunnett's multiple test vs. basal.

**3.2.2. Analysis of HR changes in VVS patient's groups**

In the subgroup of VVS patients with BP raise during IHG, HR increased from 74.5 ± 9.2 beat/min to 84.28 ± 21.9 beat/min ( $\Delta$ HR = 9.9 ± 4.18), while in patients without BP raise during IHG basal HR increased from 83.8 ± 6.3 beat/min to 85 ± 12 beat/min ( $\Delta$ HR = 3 ± 2.8 b/m), showing no significant difference between both subgroups (*p* > 0.07) (Table 3).

**3.3. Clinical data and autonomic function tests in different subgroup of VVS patients**

Age of beginning of syncope, mean number of syncope during the last 12 months and presence of postural and emotional trigger factor did not differs between patients with pressor response and without response to IHG (Table 2). There was no significant difference in response to  $\Delta$ BP,  $\Delta$ HR, VM phase II and IV, Valsalva ratio and BRS between the

subgroup of VVS patients with BP raise during IHG and the group of patients without BP raise (Table 2).

**4. Discussion**

The main findings of this work were: 1) During IHG, both healthy and VVS groups showed significantly BP increases, but in both groups the pattern of the individual contribution of CO and TPR to the pressor response was different. 2) In VVS patients, the pattern of the pressor components was different as compared with healthy subjects. In a subgroup of VVS patients, the pressor response to IHG was blunted, without increased in CO and TRP, while the cardiovascular and cardiac sympathetic function were preserved.

It is known that in healthy subjects the pressor response to IHG showed an individual pattern of CO and TPR changes, with an inverse relationship between both components, (Watanabe et al., 2014).

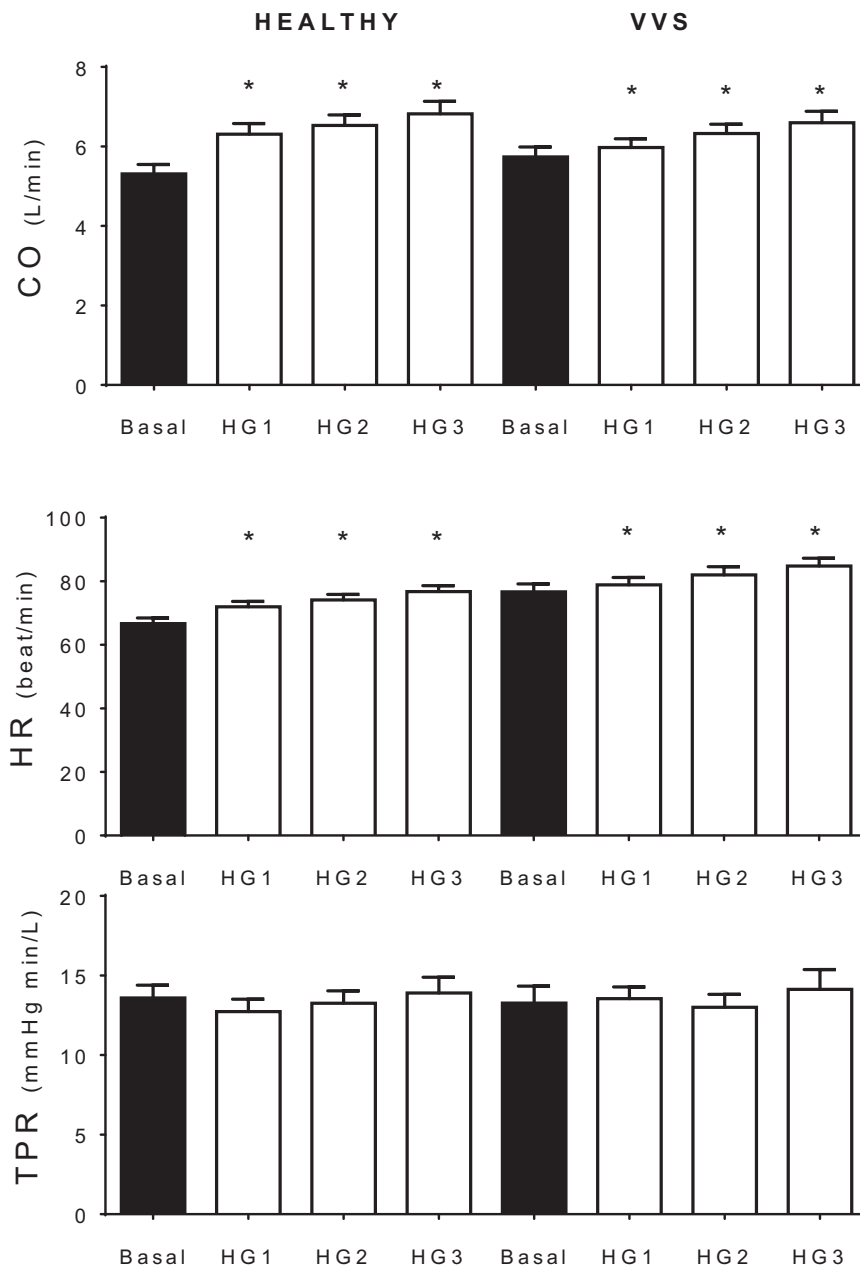


Fig. 2. Mean components of pressor response to handgrip. Mean  $\pm$  SEM: CO = cardiac output, HR = heart rate, TPR = total peripheral resistance. Basal = baseline values; HG1–3, values obtained at 1–2 and 3 min of handgrip (HG). \* $p < 0.05$ . One-way ANOVA followed by Dunnett's multiple tests basal.

Present results confirmed the occurrence of this pattern in all healthy subjects and in 81% of VVS patients. No change in BP, CO and TPR to IHG was observed in 19% VVS patients. However, this subgroup of patients without BP rise during IHG showed normal sympathetic vasoconstrictor activation to both gravitational stress and BP response to Valsalva maneuver. A plethysmography evaluation of BP change to IHG in VVS patients showed a 25% of patients with blunted BP response (Van den Berg and Smit, 1997), other study found attenuated BP response to IHG in VVS patients with history of syncope during sleep (Jardine et al., 2009).

The mechanisms involved in the pressor response and the HR increase during IHG, depends on the integrity of the exercising skeletal muscle receptors (muscle metaboreflex and mechanoreflex) (Boushel, 2010), sensory afferent pathways (III and IV muscle afferent endings), the central nervous system integration, the baroreceptor modulation, the sympathetic efferent pathways (Fadel and Raven, 2012, Fisher et al., 2015) and the end-organ receptor (e.g.  $\alpha$  and  $\beta$  adrenergic)

sensitivity (Kiviniemi et al., 2012). One study attributed the blunted pressor response in patients with VVS to an abnormal peripheral vasoconstriction (arterial and venous) (Van den Berg and Smit, 1997), while other study showing a decreased BP rise during the first minute of the isometric exercise, ascribe it to an abnormal central command regulation, occurring immediately before the metaboreflex activation (Jardine et al., 2009) In human, the main mechanisms to increase CO during IHG is the regional blood flow redistribution with increase in thoracic and decrease in splanchnic blood volume, which increase the venous return and enhanced the cardiac contractility (Stewart et al., 2007). Blunted pressor response during isometric exercise without CO increase, due to abnormal redistribution of regional blood volume may explain our findings. The vasomotor activity of splanchnic vasculature depends on the nitric oxide (NO) modulation of adrenergic vasoconstriction. In young VVS patients in supine position, there is an excessive nitric oxide (NO) production within the splanchnic circulation, which impaired the adrenergic vasoconstriction (Stewart et al., 2016). In

**Table 2**  
Autonomic function tests in subgroups of VVS patients that increased or not the arterial blood pressure in response to isometric handgrip.

	IHG BP rise	IHG no BP rise	p
n	26	6	
Sex female	21	6	
Age (years)	28.5 ± 2.5	27.7 ± 6.9	0.303
BRS	8.6 ± 0.9	7.9 ± 1.2	0.570
Valsalva ratio	1.8 ± 0.1	1.4 ± 0.1	0.397
VVS history			
Beginning (years)	16.6 ± 3.8	12.6 ± 4.8	0.150
Syncope (last 12 months)	2.3 ± 0.6	2.4 ± 0.54	0.700
Postural triggered	26/26	6/6	1.000 #
Emotional triggered	8/26	3/6	0.371 #
Supine			
SBP (mm Hg)	115.0 ± 2.2	119.2 ± 1.8	0.369
HR (beat/min)	74.8 ± 1.6	80.7 ± 5.3	0.135
Orthostatic change			
Δ SBP (mm Hg)	6.7 ± 2.3	−0.7 ± 0.4	0.231
HR (beat/min)	10.4 ± 1.7	12.0 ± 3.6	0.807

Mean ± SEM. BRS = baroreflex sensitivity, SBP = systolic blood pressure, DBP = diastolic blood pressure, Δ SBP = systolic blood pressure increase. HR = heart rate. p corresponds to Student unpaired test, IHG BP rise vs BP no rise, and # to Chi square test.

**Table 3**  
Distribution of individual components of pressor response to isometric handgrip in of health subjects and VVS patients.

	Healthy subjects	VVS patients
n	30	32
Increased CO	16 (53.6%)	14 (43.8%)
Increased TRP	7 (23.3%)	10 (31.3%)
Increased both CO and TRP	7 (23.3%)	2 (6.2%)
No increased CO or TRP	0 (0.00%)	6 (18.8%)

Chi square test.  $p > 0.0246$ .

addition, a defective central command activation during IHG could be responsible for the blunted pressor response in our patients.

Patients without pressor response during IHG showed preserved baroreceptors and cardiopulmonary responses to the sudden fall of CO during the Valsalva maneuver, and normal cardiovagal modulation during and after the maneuver.

Baroreflex sensitivity was lower in our VVS patients compared with healthy subjects, but no difference in such baseline subtle dysfunction was found between VVS subgroups with and without pressor response during IHG. Moreover, during orthostatic stress, the arterial baroreflexes in VVS patients were able to compensate the initial CO fall, possibly a posterior fail of these reflexes may contribute to the transient hypotension and bradycardia (Jardine, 2013).

In VVS, isometric exercise can abort the syncope, if the patient recognizes the prodromal symptoms and perform isometric arm contractions increasing BP and HR, could avoid losing consciousness (Crocì et al., 2004). This physical-counter maneuver is not useful in the subgroup of VVS patients with blunted pressor response to IHG.

Limitations of this study are: the method of beat-to-beat photoplethysmography used to measure BP and stroke volume (derived by a computer algorithm) from arterial waveform, which is very similar to that from invasive brachial artery catheter (Imholz et al., 1998). The assessment of CO and TPR by this method only gives trends, but not absolute values. Nevertheless, we found a pattern of individual responses of CO and TPR during IHG in healthy subjects, like what was observed using a Doppler ultrasound method (Watanabe et al., 2014). We did not measure regional blood flow and blood volume, a study with impedance plethysmography could add valuable information. Due to

the small number of patients without pressor response to IHG it was not possible to characterize baseline clinical difference between subgroups.

## 5. Conclusions

Our study demonstrates that, a subgroup of 19% of patients with VVS show blunted pressor response to IHG, and VVS patients have a different pattern of the individual distributions of CO and TPR changes, from healthy subjects. Present results suggest that VVS patients present an abnormal regulation of cardiovascular responses to IHG, with preserved cardiovagal and cardiac sympathetic function. The finding of abnormal BP response to isometric exercise may help to characterize a subgroup of VVS patients without benefit of isometric maneuver to abort syncope.

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## References

Bogert, L.W., Wesseling, K.H., Schraa, O., Van Lieshout, E.J., de Mol, B.A., van Goudoever, J., Westerhof, B.E., van Lieshout, J.J., 2010. Pulse contour cardiac output derived from non-invasive arterial pressure in cardiovascular disease. *Anaesthesia* 65 (11), 1119–1125.

Boushel, R., 2010. Muscle metaboreflex control of the circulation during exercise. *Acta Physiol. (Oxf.)* 199 (4), 367–383.

Crocì, F., Brignole, M., Menozzi, C., Solano, A., Donato, P., Oddone, D., et al., 2004. Efficacy and feasibility of isometric arm counter-pressure maneuvers to abort impending vasovagal syncope during real life. *Europace* 6 (4), 287–291.

Fadel, P.J., Raven, P.B., 2012. Human investigations into the arterial and cardiopulmonary baroreflexes during exercise. *Exp. Physiol.* 97 (1), 39–50.

Fisher, J.P., Young, C.N., Fadel, P.J., 2015. Autonomic adjustments to exercise in humans. *Compr. Physiol.* 5 (2), 475–512.

Guieu, R., Deharo, J.C., Ruf, J., Mottola, G., Kipson, N., Bruzzese, L., et al., 2015. Adenosine and clinical forms of neurally-mediated syncope. *J. Am. Coll. Cardiol.* 66 (2), 204–205.

Imholz, B.P., Wieling, W., van Montfrans, G.A., Wesseling, K.H., 1998. Fifteen years' experience with finger arterial pressure monitoring: assessment of the technology. *Cardiovasc. Res.* 38 (3), 605–616.

Jardine, D.L., 2013. Vasovagal syncope: new physiologic insights. *Cardiol. Clin.* 31 (1), 75–87.

Jardine, D.L., Krediet, C.T., Cortelli, P., Frampton, C.M., Wieling, W., 2009 Sep 7. Sympathovagal responses in patients with sleep and typical vasovagal syncope. *Clin. Sci. (Lond.)* 117 (10), 345–353.

Jardine, D.L., Wieling, W., Brignole, M., Lenders, J.W.M., Sutton, R., Stewart, J., 2017. Pathophysiology of the vasovagal response. *Heart Rhythm.* S1547–5271 (17), 31434–0.

Khurana, R.K., Setty, A., 1996. The value of the isometric hand-grip test—studies in various autonomic disorders. *Clin. Auton. Res.* 6 (4), 211–218.

Kiviniemi, A.M., Frances, M.F., Rachinsky, M., Craen, R., Petrella, R.J., Huikuri, H.V., et al., 2012. Non-alpha-adrenergic effects on systemic vascular conductance during lower-body negative pressure, static exercise and muscle metaboreflex activation. *Acta Physiol. (Oxf.)* 206 (1), 51–61.

Longin, E., Reinhard, J., von Buch, C., Gerstner, T., Lenz, T., König, S., 2008. Autonomic function in children and adolescents with neurocardiogenic syncope. *Pediatr. Cardiol.* 29 (4), 763–770.

Mosqueda-Garcia, R., Furlan, R., Tank, J., Fernandez-Violante, R., 2000. The elusive pathophysiology of neurally mediated syncope. *Circulation* 102 (23), 2898–2906.

Sheldon, R.S., Grubb, B.P., Olshansky, B., Shen, W.K., Calkins, H., Brignole, M., et al., 2015 Jun. 2015 heart rhythm society expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope. *Heart Rhythm.* 12 (6), e41–63.

Shinohara, T., Ebata, Y., Ayabe, R., Fukui, A., Okada, N., Yufu, K., et al., 2014. Cardiac autonomic dysfunction in patients with head-up tilt test-induced vasovagal syncope. *Pacing Clin. Electrophysiol.* 37 (12), 1694–1701.

Stewart, J.M., Montgomery, L.D., Glover, J.L., Medow, M.S., 2007. Changes in regional blood volume and blood flow during static handgrip. *Am. J. Physiol. Heart Circ. Physiol.* 292 (1), H215–23.

Stewart, J.M., Suggs, M., Merchant, S., Sutton, R., Terilli, C., Visintainer, P., et al., 2016. Postsynaptic α1-adrenergic vasoconstriction is impaired in young patients with vasovagal syncope and is corrected by nitric oxide synthase inhibition. *Circ. Arrhythm. Electrophysiol.* 9 (8) (pii: e003828).

Vaddadi, G., Guo, L., Esler, M., Socratous, F., Schlaich, M., Chopra, R., et al., 2011. Recurrent postural vasovagal syncope: sympathetic nervous system phenotypes. *Circ. Arrhythm. Electrophysiol.* 4 (5), 711–718.

Van den Berg, M.P., Smit, A.J., 1997. Bedside autonomic function testing in patients with vasovagal syncope. *Pacing Clin. Electrophysiol.* 20 (8 Pt 2), 2039–2042.

Watanabe, K., Ichinose, M., Tahara, R., Nishiyasu, T., 2014. Individual differences in cardiac and vascular components of the pressor response to isometric handgrip exercise in humans. *Am. J. Physiol. Heart Circ. Physiol.* 306 (2), H251–60.

Zygmunt, A., Stanczyk, J., 2004. Heart rate variability in children with neurocardiogenic syncope. *Clin. Auton. Res.* 14 (2), 99–106.