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Research paper

Influence of repetitions on the Valsalva maneuver

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ABSTRACT

Objective: In autonomic units, patients perform several short Valsalva maneuvers (VMs) while learning the procedure. The effects of repeated VMs on cardiovascular elicited responses were assessed.
Methods: 14 healthy volunteer subjects were selected (aged 22–26). VMs were performed every 3 min up to 6 times in a reclined sitting position. Changes in blood pressure (BP), heart rate (HR) and baroreflex sensitivity indexes were evaluated. Subjects were classified according to their adrenergic response patterns.
Results: VMs repetitions evoked a progressive decrease in BP during phases II and III and a reduced increase in mean BP at late phase II. Increased bradycardia at early phase II and IV was also observed. Last two VMs showed a significant increase in Valsalva ratio, while other indexes remained unaltered. Subjects with balanced adrenergic responses presented extended pressure recovery time from the third repetition and lower BP values than those with augmented or suppressed adrenergic responses.
Conclusions: Significant changes in BP and HR at certain phases were observed when consecutive VMs were performed in young subjects in a reclined position. The most affected baroreflex index was the Valsalva ratio. Adrenergic response patterns showed differences that should be considered in order to avoid false positives.
Significance: We recommend not repeating the VM more than 4 times and revisiting the role and reliability of the Valsalva ratio.
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1. Introduction

The Valsalva maneuver (VM), defined as a forced expiration while blocking air outflow, is named after the Italian physician MA Valsalva. The subject exhales with an open glottis against a mouthpiece connected to a pressure manometer that allows to estimate a constant alveolar pressure, generating a predictable intrathoracic pressure (Hilz and Dutsch, 2006; Junqueira, 2008). Changes in intrathoracic and intra-abdominal pressure induce a pressure response, activating cardiovascular and neuroendocrine systems (Pstras et al., 2016). An agreed protocol of 40 mmHg expiratory pressure with a duration of 15 or 20 s is usually employed (Junqueira, 2008).

Many clinical applications of VM have been described in medical practice, although its role in the diagnosis and monitoring of dysautonomia is noteworthy. Throughout this maneuver, changes in venous return, cardiac output and blood pressure trigger the baroreceptor reflex, activating or inhibiting brainstem nuclei involved in sympathetic and parasympathetic outflow (Cooke et al., 2002), thus allowing the dynamic assessment of autonomic activity. The VM is usually used together with other standardized tests that constitute the autonomic evaluation protocol (Gibbons et al., 2017; Low, 2003; Ziemssen and Siepmann, 2019). The most basic analysis is obtained from an ECG recording of heart rate changes that occur during the maneuver (Junqueira, 2008). A more complete and reliable evaluation requires the simultaneous and continuous recording of blood pressure, which can be measured either invasively or, more commonly, non-invasively using digital optical plethysmography (Goldstein and Cheshire, 2017).

The VM offers some technical advantages; it is non-invasive, low-cost, short lasting, does not require a specialized laboratory, can be applied in outpatients and entails very low risk

Abbreviations: VM, Valsalva maneuver; PI, PII, PIII, PIV, phases I to IV; PII_E, PII_L, early and late phase II; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; PP, pulse pressure; HR, heart rate; HRV, heart rate variability; HF, high frequency; LF, low frequency; VR, Valsalva ratio; PRT, pressure recovery time; BRSa, adrenergic baroreflex sensitivity; BRSv, vagal baroreflex sensitivity; BRSg, global baroreflex sensitivity; AAR, augmented autonomic response; BAR, balanced autonomic response; SAR, suppressed autonomic response.

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(Junqueira, 2008). Adverse effects are extremely rare and include dizziness, headache, nausea, blurred vision, chest pain, syncope, hypotension or severe hypertension, arrhythmias or stroke (Pstras et al., 2016). These secondary effects are limited to high risk population, that is, patients with coronary or cerebrovascular disease (Junqueira, 2008; Levin, 1966).

Deviations in blood pressure and heart rate responses from the normal pattern are analyzed according to four well-differentiated phases (I-IV) (Hamilton et al., 1936). An example of how these phases are delimited in a normal VM record is shown in Fig. 1.

Phase I (PI) occurs during the first 2–3 s of straining and it is characterized by a brief increase in blood pressure and a slight bradycardia due to the increase in intrathoracic pressure that drives blood to the peripheral territories (Eckberg, 1980; Hilz and Dutsch, 2006).

Phase II is divided into early (PII_E) and late (PII_L). During the early phase II there is a progressive decrease in blood pressure due to a lower venous return and, therefore, lower cardiac output (Looga, 2005). This pressure drop inhibits the baroreflex discharge, which results in increased sympathetic activity and, consequently, tachycardia and vasoconstriction are elicited, leading to augmented peripheral resistances and increasing blood pressure (Hilz and Dutsch, 2006). This response corresponds to late phase II and is highly dependent on α-adrenergic activation (Sandroni et al., 1991).

Phase III begins at the end of expiration and lasts 1–2 s. It is due to an abrupt drop of intrathoracic pressure that increases venous return into the thorax. Thoracic blood vessels are expanded and this causes a sudden fall in blood pressure (Looga, 2005). Reflex tachycardia and vasoconstriction generated at phase II are maintained and potentiated (Hamilton et al., 1936).

The greater intrathoracic blood volume contributes to an increase in diastolic ventricular filling. This higher preload induces an increase in systolic volume and cardiac output, as explained by the Frank-Starling mechanism. As peripheral resistances are still high, due to sustained vasoconstriction, it results in an important increase in blood pressure called overshoot, which characterizes phase IV (Sarnoff et al., 1948). This phase is less dependent on vasoconstriction and relies mainly on β-adrenergic stimulation (Sandroni et al., 1991).

The overshoot induces a strong baroreceptor activation which generates a marked vagal bradycardia and a vasodilation secondary to the decreased sympathetic flow. Blood pressure progressively decreases, although it remains elevated for a considerable time, partly due to the release of circulating catecholamines (Looga, 2005; Sandroni et al., 2000).

VM phases may show different characteristics than those cited before in normal population. Palamarchuk et al. (2016) described three normal VM response patterns depending on the adrenergic basal tone and the adrenergic response during phase II (Fig. 2).

Since a variety of factors have been shown to modify the normal patterns of the maneuver, several studies analyzing VM methodology have been carried out. The effects of very long-lasting bed rest (Shoemaker et al., 2003), body position before and during the maneuver—standing, sitting or supine—(Singer et al., 2001; Ten Harkel et al., 1990), previous inspiration or expiration (Looga, 2005), straining duration and level of airway pressure (Benarroch et al., 1991), changes in plasma volume (Fritsch-Yelle et al., 1999) or intrathoracic blood volume (Stewart et al., 2004) have been studied. In addition, there are other factors that have been described such as age, time of the day, room temperature and humidity, previous liquid or food intake, or the consumption of stimulants or medication (Pstras et al., 2016).

One of the factors that have not been analyzed yet is the effect of the number of VM repetitions that the subject performs. In fact, certain patients may have to perform several short maneuvers to learn the technique, to train it or because of unsuccessful straining or suboptimal responses. There is no specific published research about this topic, although some authors have recommended a maximum of four repetitions (Hilz and Dutsch, 2006; Junqueira, 2008).

In this study, we have analyzed the effects of repeating Valsalva maneuvers up to six times in the reclined sitting position to detect which phases can be modified and which could be the possible influence on baroreflex indexes. Our intention was to provide with methodological recommendations about a maximum number of repetitions.

2. Methods

2.1. Subjects

This quasi-experimental study was designed as a pretest-posttest research without control group. Fourteen healthy volunteers (7 men and 7 women), aged 22–26 years, took part in this study. All the subjects were naïve, and none had been previously trained in performing the Valsalva maneuver. Previous informed consent was obtained in all cases. Exclusion criteria were previous pathologies (including history of syncope or orthostatic intolerance), high-level training, pregnancy or toxic habits. The protocol was approved by the Research Ethics Committee of the province of Málaga (Andalucía, Spain).

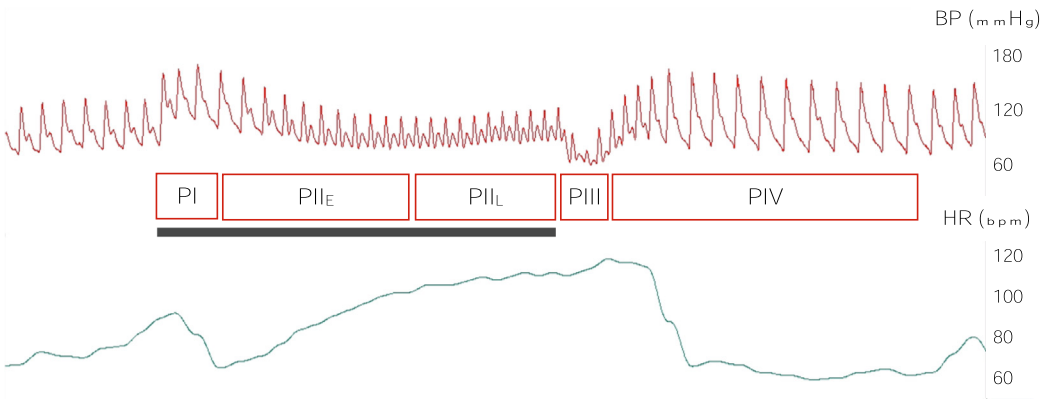

Fig. 1. Continuous arterial blood pressure (BP, superior panel) and heart rate (HR, inferior panel) recording during the Valsalva manoeuvre in subject no. 11. Middle panel shows VM phases: Phase I (PI), early Phase II (PII_E), late Phase II (PII_L), Phase III (PIII) and Phase IV (PIV). The shaded area indicates the straining time (15 s, 40 mmHg).

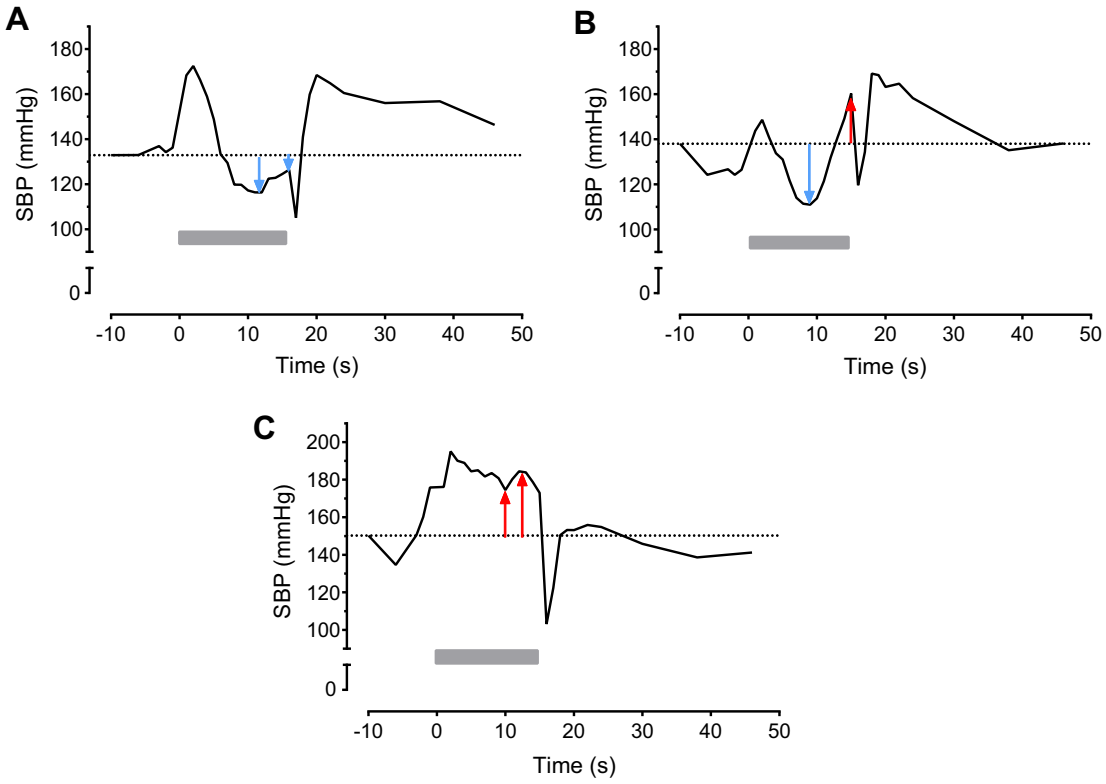

Fig. 2. Examples of different adrenergic response patterns in three subjects. The dotted line shows baseline systolic blood pressure (SBP). The first and second arrow in every graph indicates the minimum SBP value at early phase II and the maximum SBP value in late phase II, respectively. A: balance adrenergic response (BAR). B: augmented autonomic response (AAR). C: supressed autonomic response (SAR). The shaded area indicates the straining time (15 s, 40 mmHg).

2.2. Procedure

Each subject was monitored for 10 min at rest and 20 min of intervention in reclined sitting position (60°). Volunteers were instructed to blow against a mouthpiece connected to a BigBen Riester® manometer for visual feedback at a constant pressure of 40 mmHg for 15 s. Subjects performed six VM (V1, V2…, V6) with 3-minutes rest intervals between maneuvers.

Standard conditions of temperature (24 °C) and relative humidity (30%) were maintained in the autonomic laboratory. Studies were performed at the same time of day (5:30 PM). Subjects were advised to avoid physical exercise and not to eat or drink in the previous two hours. The volunteers were cam recorded during the procedure.

2.3. Variables

Continuous beat-to-beat non-invasive blood pressure (BP) (Nexfin®, BMeye), heart rate (HR) (Cardioline-Delta 1 Plus®) and airway expiratory pressure (Riester®) were digitalized with the BIOPAC® MP-160 CE converter and analyzed with AcqKnowledge 4.2 signal analysis software.

Mean heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean blood pressure (MBP) values were measured at 20–30 s prior to each maneuver. These were considered as baseline values. The same parameters were also recorded every second from −10 sec to + 45 sec, considering second 0 as the beginning of the straining. The values corresponding to each of the phases (PI, PII_E, PII_L, PIII and PIV) were calculated. Subjects were classified afterwards according to the three adrenergic response patterns: BAR, AAR or SAR.

According to Novak's published suggestions, the following variables were calculated (Novak, 2011): maximal MBP drop during PII_E (difference between baseline MBP and minimum MBP in PII_E), MBP recovery at PII_L (difference between baseline MBP and maximum MBP at PII_L), MBP increase at PIV or overshoot (difference between baseline MBP and maximum MBP at PIV), maximum pulse pressure (PP) drop at PII (%), SBP recovery time or PRT (time in seconds to reach baseline SBP from PIII) and Valsalva ratio (relation between maximum HR during PII_L-PIII and minimum during PIV).

Adrenergic (BRSa), vagal (BRSv) and global (BRSg) baroreflex sensitivities were also calculated according to the criteria of the group of P. Low and Mayo Clinic recommendations (Schrezenmaier et al., 2007). BRSa (mmHg/s) was determined by the formula (A + B * 0.75)/PRT, where A is the SBP drop at PII_E and B is the difference between maximum SBP at PII_L and minimum SBP at PIII. BRSv (milliseconds/mmHg) was defined as the regression curve slope between the RR interval expressed in milliseconds and SBP values during PII_E. BRSg results from the product of BRSa and BRSv (ms/s). Normative data adjusted by age were obtained from Huang et al. (2007), Mathias et al. (2013), and Novak (2011).

Heart rate variability analysis in the frequency domain (HRV) using the autoregressive model (AR) was also performed. Power values in high frequency (HF, 0.15–0.4 Hz) and low frequency (LF, 0.04–0.15 Hz) bands expressed in absolute values (ms^2) and normalized units (nu), as well as LF/HF relation were obtained using Kubios HRV Standard 3.2.

2.4. Statistical analysis

Data processing was carried out using statistical package SPSS Statistics 25 (IBM) and Prism 6 (GraphPad). Descriptive analysis of quantitative variables was performed, obtaining mean, standard deviation, minimum and maximum for each parameter.

For analytical statistics, data were grouped into three comparison groups according to pairs of VM repetitions (1–2 vs 3–4 and

5–6). The significance level was established at $p < 0.05$. Nonparametric tests were used; Mann-Whitney *U* test for independent quantitative variables (demographic statistics and adrenergic pattern comparison) and Friedmann test for paired quantitative variables. Dunn test was used as a posthoc test for multiple comparisons after Friedmann test (adjusted p values < 0.05 were considered significant).

Table 1
Demographic characteristics and HRV.

	Male (n = 7)	Female (n = 7)	Mann Whitney p value
Age – years	24,29 ± 1,25 (23–26)	23,29 ± 0,76 (22–24)	0,165
Height – cm	173,29 ± 6,29 (165–184)	165,00 ± 7,48 (154–174)	0,073
Weight – kg	66,86 ± 8,19 (57–80)	61,49 ± 12,69 (45–83)	0,383
BMI – kg/m^2	22,36 ± 1,66 (20,40–25,40)	22,57 ± 3,39 (17,80–27,90)	0,99
BSA – m^2	1,81 ± 0,13 (1,64–2,00)	1,68 ± 0,20 (1,42–2,00)	0,259
SBP – mmHg	116,43 ± 4,76 (110–120)	115,71 ± 5,35 (110–120)	0,902
DBP – mmHg	70,00 ± 5,77 (60–80)	76,86 ± 8,61 (70–90)	0,128
LF – n.u.	66,51 ± 17,24 (36,42–88,18)	61,81 ± 8,85 (46,91–73,52)	0,338
HF – n.u.	33,45 ± 17,23 (11,80–63,54)	38,10 ± 8,88 (26,37–53,05)	0,338
LF/HF	2,85 ± 2,29 (0,57–7,47)	1,75 ± 0,64 (0,88–2,79)	0,338

Results are shown as mean ± standard deviation (min–max).
HRV: heart rate variability; BMI: body mass index; BSA: body surface area; SBP: systolic blood pressure; DBP: diastolic blood pressure; LF: low frequency band; HF: high frequency band; n.u. normalized units; LF/HF: sympatovagal balance.

3. Results

Demographic characteristics and HRV analysis of volunteers (n = 14) are shown in Table 1. There were no significant differences between men and women.

No differences were found for airway pressure and duration of the different VMs (Table 2). All subjects were able to complete the experimental protocol.

Baseline BP and HR values before each maneuver are shown in Table 2. No differences between VMs were observed in baseline BP after six repetitions. HR values decreased in the last two VMs ($p < 0.01$).

A non-significant progressive decrease of mean SBP, DBP, MBP and HR was observed with VM repetitions throughout all the phases (Table 2, Fig. 3). BP changes were significant at phases PII_E, PII_L and PIII, and HR changes at phases PII_E and PIV when comparing V5-V6 vs V1-V2. MBP increase at PII_L was decreased in V5-V6 ($p = 0.005$). No significant differences in the MBP drop at PII_E, the MBP increase at PIV and the PP drop at PII_E were observed (Table 3, Fig. 3).

There was a significant increase of Valsalva ratio (VR) in maneuvers V5-V6 ($p = 0,016$). No significant differences were observed in PRT, BRSa, BRSv or BRSg with VM repetitions (Table 3).

A subgroup analysis was also carried out according to Palamarchuk's patterns of adrenergic responses. 7 subjects were classified as BAR (50%), 6 subjects as AAR (43%) and 1 subject as SAR (7%). Because of the similarity of their increased adrenergic activ-

Table 2
Blood pressure and heart rate responses to repeated Valsalva maneuvers.

		V1-V2 (I)	V3-V4 (II)	V5-V6 (III)	Dunn p value I vs II/I vs III
Straining time (s)		15,36 ± 0,37	15,32 ± 0,35	15,29 ± 0,35	ns/ns
Airway pressure (mmHg)		38,99 ± 2,02	39,22 ± 2,04	39,36 ± 1,99	ns/ns
Baseline					
	SBP	146,19 ± 13,40	144,26 ± 13,51	142,06 ± 15,54	ns/ns
	DBP	72,79 ± 8,61	72,30 ± 9,24	71,90 ± 10,03	ns/ns
	MBP	101,88 ± 9,70	101,51 ± 10,84	100,38 ± 12,08	ns/ns
	HR	77,79 ± 10,02	76,17 ± 8,35	74,63 ± 9,86	ns/0,0092†
Phase I					
	SBP	161,55 ± 26,54	161,89 ± 37,30	155,38 ± 26,64	ns/ns
	DBP	109,22 ± 11,86	106,98 ± 11,71	103,74 ± 10,32	ns/ns
	MBP	134,71 ± 12,38	133,67 ± 15,65	129,83 ± 11,55	ns/0,0281*
	HR	95,76 ± 14,24	94,86 ± 13,99	91,59 ± 12,19	ns/ns
Early phase II					
	SBP	123,97 ± 20,18	121,32 ± 21,89	114,40 ± 23,44	ns/0,005†
	DBP	84,21 ± 12,62	81,56 ± 12,72	76,39 ± 12,19	ns/0,0007†
	MBP	99,75 ± 13,84	97,31 ± 14,45	90,76 ± 14,50	ns/0,0013†
	HR	79,34 ± 15,11	75,78 ± 13,18	74,26 ± 11,97	ns/0,0164*
Late phase II					
	SBP	148,30 ± 23,95	142,39 ± 20,29	139,10 ± 25,93	ns/0,0468*
	DBP	107,07 ± 18,12	103,34 ± 14,10	98,87 ± 18,54	ns/0,0281*
	MBP	119,99 ± 19,43	114,96 ± 14,93	112,48 ± 17,85	ns/0,0281*
	HR	113,65 ± 17,61	112,80 ± 17,33	114,16 ± 17,62	ns/ns
Phase III¶					
	SBP	113,99 ± 22,89	107,96 ± 18,60	104,27 ± 22,93	ns/0,0164*
	DBP	78,25 ± 13,88	75,92 ± 10,59	73,68 ± 14,76	ns/0,0281*
	MBP	95,33 ± 20,42	90,81 ± 16,86	87,93 ± 20,10	ns/0,0003†
Phase IV					
	SBP	174,11 ± 20,37	172,16 ± 17,25	170,00 ± 17,99	ns/ns
	DBP	98,39 ± 13,59	96,95 ± 11,52	95,01 ± 10,98	ns/ns
	MBP	127,19 ± 15,89	125,59 ± 14,67	122,91 ± 14,56	ns/ns
	HR	67,02 ± 14,80	62,39 ± 11,12	60,31 ± 9,49	ns/0,005†

V(n)-V(n + 1): mean ± SD values of two consecutive repetitions of the Valsalva maneuver; SBP: systolic blood pressure (mmHg); DBP: diastolic blood pressure (mmHg); MBP: mean blood pressure (mmHg); HR: heart rate (bpm).
ns: non-significant; *p < 0,05; † p < 0,01.
¶ HR at this phase was not measured as it was considered as a continuation of PII_L HR.

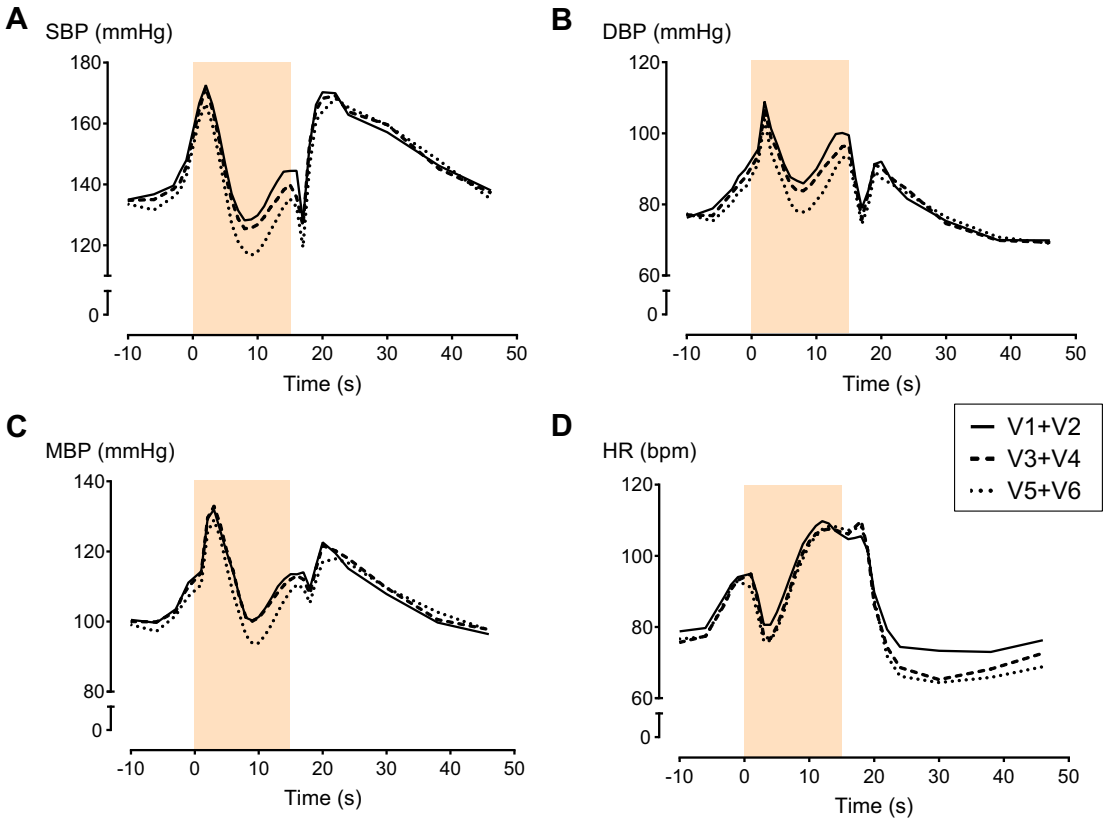

Fig. 3. Mean values of systolic BP (A), diastolic BP (B), mean BP (C) and heart rate (D) for every VM pair (n = 14). The shaded area indicates the straining time (15 s, 40 mmHg).

Table 3
Cardiovascular responses and changes in baroreflex indexes.

		Normative values†	V1-V2 (I)	V3-V4 (II)	V5-V6 (III)	Dunn p value IvsII/IIvsIII
Baroreflex indexes	MBP drop at PII_E	> 20 mmHg	35.35 ± 5.92	36.60 ± 7.85	39.09 ± 9.87	ns/ns
	PP drop (%)	> 50%	40.63 ± 15.66	39.74 ± 17.04	41.53 ± 16.71	ns/ns
	MBP increase at PII_L	> 0 mmHg	17.13 ± 12.70	13.44 ± 10.87	11.53 ± 12.21	ns/0.005*
	MBP increase at PIV	> 0 mmHg	26.25 ± 9.46	25.06 ± 8.08	23.41 ± 9.77	ns/ns
	Valsalva ratio	1.6–2.08	1.73 ± 0.28	1.79 ± 0.28	1.88 ± 0.28	ns/0.0164*
	PRT (s)	0.21–2.89	1.34 ± 0.49	1.38 ± 0.48	1.51 ± 0.63	ns/ns
	BRSa (mmHg/s)	15.1–182.6	43.84 ± 24.73	41.09 ± 23.53	42.66 ± 19.19	ns/ns
	BRSv (ms/mmHg)	3.5–22.3	4.99 ± 1.85	5.48 ± 2.48	5.55 ± 2.75	ns/ns
	BRSg (ms/s)	116–2123	206.53 ± 100.86	197.52 ± 115.11	224.49 ± 129.43	ns/ns

V(n)-V(n + 1): mean ± SD values of two consecutive repetitions of the Valsalva maneuver; MBP: mean blood pressure (mmHg); PP: pulse pressure; PRT: pressure recovery time; BRSa: adrenergic baroreflex sensitivity; BRSv: vagal baroreflex sensitivity; BRSg: global baroreflex sensitivity.
ns: non-significant; * p < 0,05.
† Normative values from (Huang et al., 2007; Mathias et al., 2013; Novak, 2011)

ity, AAR and SAR subjects were grouped into a single category. Significant differences of SBP, DBP and MBP at phases PII_E, PII_L and PIII were observed in the six VMs performed (Table 4, Fig. 4). A significant lower MBP increase at PII_L and a longer PRT were observed when comparing BAR vs AAR + SAR subjects at V3-V4 and V5-V6 (Table 4, Fig. 5).

It is also noticeable that the switch from bradycardia to tachycardia at phase II_E appears always around the fourth second during the VM, while the point of inflexion to a pressor response in diastolic BP at phase II_L is consistently seen around the seventh-eighth second (Fig. 3).

4. Discussion

The main observation of this study is that repetitions of VM induce a progressive significant increase of VR with little changes in other baroreflex indexes, an effect which is more evident after the fifth repetition.

Establishing standardized conditions for the Valsalva maneuver is key to obtain reproducible and reliable measurements for clinical evaluation. The most widespread protocol for VM autonomic evaluation indicates a forced expiration in the supine position, reaching an airway pressure of 40 mmHg for 15 s (Hilz and Dutsch, 2006; Junqueira, 2008; Looga, 2005; Low, 2003; Ziemssen and Siepmann, 2019). The maneuver has to be repeated until obtaining two curves with similar results (Low, 2003). Some authors lengthen the maneuver up to 20 s, thus obtaining a more powerful stimulus (Junqueira, 2008). However, to avoid adverse reactions in subjects with high risk factors it is preferable to use the 15-seconds protocol (Junqueira, 2008). Regarding the level of airway pressure, a 40 mmHg target value is accepted by the majority of researchers, although one study suggests that 60% of the

Table 4
Cardiovascular responses according to the adrenergic response patterns (mean ± SD).

		BAR			AAR + SAR			Mann-Whitney p value IvsIV/IIvsV/IIIvsVI
		V1-V2 (I)	V3-V4 (II)	V5-V6 (III)	V1-V2 (IV)	V3-V4 (V)	V5-V6 (VI)	
Baseline								
	SBP	145,67 ± 9,54	142,48 ± 9,01	139,75 ± 8,43	146,71 ± 17,25	146,05 ± 17,52	144,39 ± 20,98	ns/ns/ns
	DBP	69,90 ± 6,02	69,49 ± 8,82	68,02 ± 6,62	75,70 ± 10,24	75,12 ± 9,42	75,80 ± 11,78	ns/ns/ns
	MBP basal	99,52 ± 5,19	98,82 ± 7,80	96,68 ± 7,01	104,25 ± 12,82	104,22 ± 13,31	104,10 ± 15,33	ns/ns/ns
	HR	74,56 ± 4,39	73,30 ± 6,59	70,37 ± 4,33	81,03 ± 13,19	79,05 ± 9,41	78,91 ± 12,23	ns/ns/ns
Phase I								
	SBP	156,59 ± 23,63	154,88 ± 27,17	154,39 ± 24,82	166,51 ± 30,17	168,90 ± 46,49	156,38 ± 30,33	ns/ns/ns
	DBP	101,44 ± 4,05	101,14 ± 8,02	98,36 ± 6,26	117,01 ± 12,14	112,83 ± 12,38	109,14 ± 11,14	0 ,011*/ns/0,038*
	MBP	127,01 ± 4,95	124,97 ± 8,97	124,35 ± 6,53	142,42 ± 13,02	142,39 ± 16,54	135,32 ± 13,28	ns/ns/ns
	HR	94,00 ± 7,52	93,31 ± 6,88	89,83 ± 8,32	97,53 ± 19,39	96,42 ± 19,28	93,37 ± 15,68	ns/ns/ns
Early phase II								
	SBP	110,80 ± 9,88	107,32 ± 11,90	101,80 ± 13,28	137,15 ± 19,50	135,31 ± 20,97	127,00 ± 25,36	0,017*/0,011*/0,038*
	DBP	76,40 ± 6,15	72,51 ± 7,53	68,80 ± 8,72	92,01 ± 12,84	90,60 ± 10,14	83,97 ± 10,57	0,017*/0,004†/0,017*
	MBP	90,85 ± 7,13	87,30 ± 8,61	82,50 ± 10,19	108,65 ± 13,39	107,32 ± 12,03	99,03 ± 13,86	0,026*/0,004†/ns
	HR	76,16 ± 10,59	72,65 ± 10,94	70,73 ± 10,03	82,53 ± 18,96	78,93 ± 15,30	77,79 ± 13,46	ns/ns/ns
Late phase II								
	SBP	134,26 ± 13,48	127,37 ± 10,62	119,49 ± 16,66	162,34 ± 24,52	157,41 ± 15,91	158,71 ± 16,80	0,026*/0,007†/0,002†
	DBP	97,22 ± 9,62	93,24 ± 7,81	85,71 ± 13,23	116,92 ± 19,82	113,44 ± 11,48	112,03 ± 12,85	0,026*/0,004†/0,007†
	MBP	108,73 ± 10,00	104,28 ± 8,11	99,03 ± 10,60	131,25 ± 20,55	125,63 ± 12,29	125,93 ± 12,47	0,026*/0,004†/0,002†
	HR	113,45 ± 13,81	114,67 ± 15,12	115,43 ± 14,58	113,85 ± 21,94	110,94 ± 20,35	112,88 ± 21,35	ns/ns/ns
Phase III								
	SBP	105,13 ± 20,65	96,72 ± 14,77	88,26 ± 15,74	122,85 ± 22,93	119,20 ± 15,39	120,28 ± 17,14	ns/0,011*/0,007†
	DBP	72,46 ± 9,77	70,32 ± 6,96	64,40 ± 7,31	84,04 ± 15,61	81,53 ± 11,02	82,96 ± 14,75	ns/ns/0,026*
	MBP	87,21 ± 13,64	82,16 ± 10,69	76,13 ± 12,03	103,45 ± 23,75	99,46 ± 18,09	99,74 ± 20,15	ns/0,038*/0,026*
Phase IV								
	SBP	172,26 ± 18,22	168,13 ± 14,00	166,81 ± 17,17	175,95 ± 23,65	176,18 ± 20,28	173,20 ± 19,56	ns/ns/ns
	DBP	93,75 ± 10,82	93,61 ± 9,75	92,23 ± 6,30	103,04 ± 15,26	100,30 ± 12,90	97,80 ± 14,25	ns/ns/ns
	MBP	124,32 ± 13,34	120,72 ± 10,13	118,92 ± 10,02	130,06 ± 18,71	130,45 ± 17,55	126,90 ± 17,93	ns/ns/ns
	FC	59,49 ± 9,01	57,79 ± 7,97	56,82 ± 7,56	74,55 ± 16,16	66,99 ± 12,46	63,80 ± 10,46	0,038*/ns/ns
VM calculated parameters								
	MBP drop at PII_E	36,78 ± 4,94	38,12 ± 8,14	42,36 ± 9,36	33,92 ± 6,84	35,07 ± 7,87	35,81 ± 9,92	ns/ns/ns
	PP drop (%)	49,40 ± 8,80	49,16 ± 11,77	47,81 ± 8,96	31,87 ± 16,58	30,31 ± 16,83	35,25 ± 20,79	0,017*/ns/ns
	MBP increase at PII_L	9,21 ± 8,93	5,46 ± 7,45	1,23 ± 6,23	25,05 ± 11,09	21,41 ± 7,21	21,83 ± 6,05	0,017*/0,004†/0,001†
	MBP increase at PIV	26,11 ± 9,96	23,13 ± 7,98	23,75 ± 10,21	26,40 ± 9,74	27,00 ± 8,32	23,07 ± 10,12	ns/ns/ns
Baroreflex indexes								
	Valsalva ratio	1,89 ± 0,31	1,93 ± 0,31	1,98 ± 0,30	1,56 ± 0,14	1,66 ± 0,20	1,79 ± 0,23	0,038*/ns/ns
	PRT (s)	1,48 ± 0,43	1,65 ± 0,46	1,77 ± 0,43	1,19 ± 0,54	1,10 ± 0,33	1,24 ± 0,71	ns/0,017*/0,026*
	BRSa (mmHg/s)	42,87 ± 21,68	40,10 ± 18,24	37,47 ± 12,10	44,82 ± 29,21	42,09 ± 29,40	47,86 ± 24,25	ns/ns/ns
	BRSv (ms/mmHg)	4,81 ± 2,25	5,50 ± 2,83	5,97 ± 3,21	5,16 ± 1,51	5,46 ± 2,31	5,14 ± 2,39	ns/ns/ns
	BRSg (ms/s)	190,10 ± 89,12	201,09 ± 83,56	245,22 ± 168,08	222,98 ± 116,06	193,97 ± 147,31	203,76 ± 83,94	ns/ns/ns

V(n)-V(n + 1): mean ± SD values of two consecutive repetitions of the Valsalva maneuver; BAR: balance autonomic response; AAR: augmented autonomic response; SAR: suppressed autonomic response; SBP: systolic blood pressure (mmHg); DBP: diastolic blood pressure (mmHg); MBP: mean blood pressure (mmHg); HR: heart rate (bpm); PP: pulse pressure; PII_E: early phase II; PII_L: late phase II; PIV: phase IV; PRT: pressure recovery time; BRSa: adrenergic baroreflex sensitivity; BRSv: vagal baroreflex sensitivity; BRSg: global baroreflex sensitivity.

* $p < 0,05$; † $p < 0,01$; ns: non-significant.

¶ HR at this phase was not measured as it was considered to be a continuation of PII_L HR.

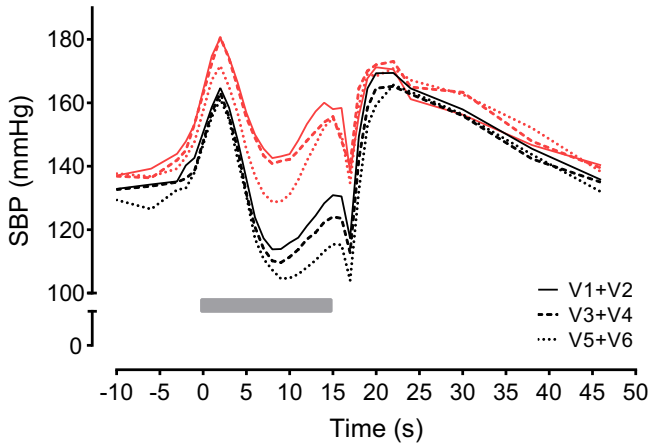

Fig. 4. Mean systolic blood pressure values for every VM pair in BAR subjects (n = 7; black) and AAR or SAR subjects (n = 7; red). The shaded area indicates the straining time (15 s, 40 mmHg). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

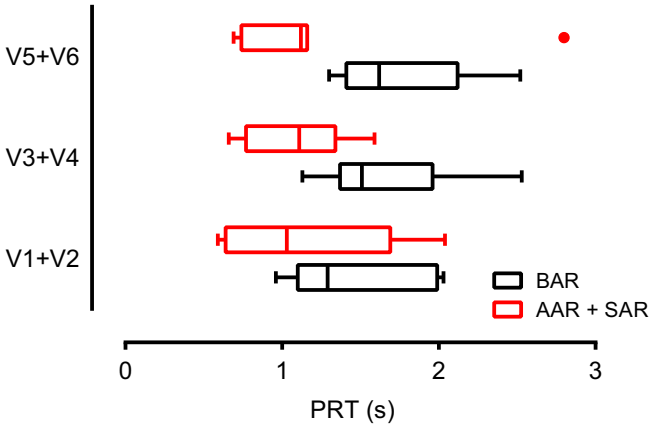

Fig. 5. PRT values according to adrenergic patterns response BAR (n = 7) and AAR + SAR (n = 7). BAR subjects showed a significant PRT lengthening after 5–6 repetitions when compared to first two repetitions ($p < 0.05$).

maximum expiratory pressure can be used to obtain the same results in subjects who are unable to maintain 40 mmHg (Paschoal et al., 2014). There are two studies analyzing exhaustively the effects of body position on the maneuver (Singer et al., 2001; Ten Harkel et al., 1990). In the supine position, a greater fall in SBP during PII_E and a smaller overshoot at PIV, with increased responses in the sitting and standing positions were described. In addition, a diminished value of BRSv under orthostatic stress was also found. No changes were described at PII_L or the VR. The authors suggest that these findings should be related with changes in venous return induced by body position (Singer et al., 2001).

In this study we aimed to analyze what changes occur when VM is repeated several times, as part of a standard protocol for autonomic evaluation. As our standard protocol is usually carried out with the patient in a reclined sitting position, we have reproduced the same conditions in this experimental design. A 3-minute delay between Valsalva maneuvers has been established.

In all VM phases, a non-significant progressive decrease of mean SBP, DBP, MBP and HR was observed with repetitions. These non-significant effects seem to be related to the phenomenon called regression toward the mean. Extreme values of the different analyzed parameters gathered around the mean with each repetition of VM. However, consecutive repetitions evoked marked alterations in certain phases of the VM.

As maneuvers are repeated, there is a significant drop in the reached values of SBP, DBP and MBP during early and late phase II. This effect could be due to a progressive accumulation of blood in the lower limbs that results in a consequent decrease of venous return with each maneuver. The decreased pool of available circulating blood volume generates a greater stimulus for the sympathetic discharge, thus facilitating the increase of blood pressure in PII_L.

However, the magnitude of the BP increase, at this phase, diminishes progressively. This effect could be attributed to a depletion of sympathetic neurotransmitter reserves at a peripheral level that leads to a progressive insufficient vasoconstriction to recover the same blood pressure values as in the first maneuvers.

Another possible and parallel mechanism may be a certain sensitization of the baroreceptors, which do not adjust their frequency of discharge in response to consecutive pressor stimuli. A decreased baroreceptor response could also explain the greater bradycardia observed in PII_E, despite the lower pressures observed in PI. On the other hand, it seems logical to obtain a decrease of BP responses in PIII when starting from lower pressure values at PII_L, this phenomenon being purely mechanical. Further research is needed to solve these issues.

The pattern of HR and BP responses also suggest that the two components of the baroreceptor reflex (HR response and peripheral vasoconstriction) show different timing. The HR component seen as tachycardia during phase II_E-II_L is visible from the fourth second, while the vasoconstriction component seen as an increase of diastolic BP becomes evident at the seventh-eighth second of the VM response. As the trigger response for the activation of the baroreflex is the same, these two timings are showing the different velocities for both components.

Despite starting from lower BP values in PIII, it should be noted that in the last maneuvers there are no significant changes in the BP overshoot values reached at PIV. This could be due to an increased cardiac adrenergic activation which compensated the decreased vasoconstriction produced in PII, thus being able to maintain the same values of overshoot during PIV (Singer et al., 2001).

The greater bradycardia observed in phase IV could be a consequence of an incremental difference of BP between phases III and IV. While the BP overshoot of phase IV remained unchanged, BP in phase III decreased progressively, thus making the BP difference more accentuated. This generates a progressive increase in baroreceptor flow to the brain stem, which results in a more marked cardiac inhibition.

Despite the previously described changes, no significant differences were found in baroreceptor sensitivity parameters (PRT, BRSa, BRSv and BRSg), which indicates the validity and reliability of these indexes for the evaluation of autonomic responses. However, a significant increase of VR was found when comparing maneuvers 5–6 with 1–2. This is explained by the greater bradycardia in PIV that progressively increases the value of the VR quotient. Therefore, it can be inferred that VR does not offer the same reliability as other indexes and perhaps it should be replaced by these baroreceptor sensitivity indexes, as some authors have pointed out (Goldstein and Cheshire, 2017).

Palamarchuk describes three different patterns of normal responses to VM (Palamarchuk et al., 2016). The most common is the balanced autonomic response (40%, BAR), in which the baseline adrenergic tone and the adrenergic response are in equilibrium. Recordings show that SBP falls below baseline during PII_E and does not exceed baseline in PII_L. The augmented autonomic response (AAR) is the second in frequency (28%). It is characterized by an increased vasomotor response during PII_L that causes SBP levels to exceed baseline in this phase. Finally, the pattern of suppressed autonomic response (15%, SAR) is characterized by a high baseline

adrenergic tone with increased vascular resistance that prevents SBP from falling below the baseline level in PII_E (Palamarchuk et al., 2016). In our study subjects were found to present similar proportions of these responses. It should be noted that subjects with AAR or SAR patterns had increased SBP, DBP and MBP levels compared to subjects with BAR patterns, probably due to a greater α-adrenergic activity. In addition, BAR subjects showed more difficulty to maintain stable values of SBP during PII_L compared to the AAR/SAR subjects, since the latter showed enough powerful compensatory responses. On the other hand, BAR subjects had longer systolic pressure recovery times (PRT) than AAR/SAR subjects that could be explained by a decreased peripheral vasoconstriction. Further research is needed to evaluate this issue.

The main limitation in this study is that the sample comprises only young subjects. We think it could be interesting to extend this study to healthy subjects and patients of different age ranges. Another limitation of this study is that the subjects were naïve participants not previously trained in how to perform Valsalva maneuvers, so a learning effect could not be definitively excluded as contributing to the changes seen. This topic should be addressed by repeating the study in trained subjects. Catecholamine measurements and cardiac output or venous peripheral resistance recordings could be of interest to solve pending issues regarding the physiological mechanisms involved in our findings. On the other hand, the sample size is comparable to other published studies and a group of female population, excluded in several studies, has been included.

5. Conclusions

In summary, we have demonstrated that, in healthy subjects in a reclined sitting position, successive repetitions of the VM induce important changes in the Valsalva ratio. This effect is more evident after the fourth repetition and affects the levels of SBP, DBP, MBP and HR. Repetitions do not alter PRT, BRSa, BRSv and BRSg. BAR, AAR and SAR patterns show differences in these responses that should be considered to avoid false positives.

We advise not to repeat the Valsalva maneuver more than four times and consider it is necessary to review the use of VR as a fundamental index of vagal cardiac activity.

Declaration of competing interest

None of the authors have potential conflicts of interest to be disclosed. All authors have approved this article.

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