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Differences in the cardiovascular hemodynamic response between the Valsalva and Reverse Valsalva Maneuvers in healthy subjects

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Abstract: Background: The Valsalva Maneuver (VM) is the first-line treatment for paroxysmal supraventricular tachycardia, but a recent, novel, and efficient tool to restore sinus rhythm has been described, i.e., the Reverse Valsalva (RV). This study aims to compare changes in cardiovascular hemodynamics and autonomic system activity (ANS) based on heart rate variability (HRV) analysis during both maneuvers.
Methods: Fifteen healthy participants performed the VM and RV maneuvers three times in a sitting position for durations of 15 s and 10 s, respectively. Blood pressure (BP) and heart rate (HR) were continuously monitored before, during and after the tests. Autonomic system activity was evaluated using frequency-domain analysis of HRV.
Results: The decrease in HR from baseline to the lowest values, expressed as a ratio, was similar during both maneuvers (0.81 during the RV vs. 0.79 during the VM, p = 0.27). However, the final lowest HR in response to the RV was higher than that in response to the VM, 70/min vs. 59/min (p <0.001). The activation of the autonomic nervous system during the most bradycardic phase of the RV (phase II) and VM (phase IV) showed that the total power of HRV was less prominent during the RV than during the VM (p <0.012), with similar levels of parasympathetic activation.
Conclusions: Our results showed less HR slowdown during the RV than during the VM. The changes in HRV parameters during both procedures in particular phases of the RV and VM suggest that the autonomic nervous system is activated alternately, so these tests can be used complementarily in a clinical setting with different results.

Keywords: supraventricular tachycardia, Vagal maneuver, Reverse Valsalva, autonomic nervous system.

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Introduction

Paroxysmal supraventricular tachycardia is a common complaint treated in the emergency department [1]. For many years, physicians using multiple maneuvers tried to cease this arrhythmia by increasing parasympathetic tone. The effect of vagal stimulation is a decrease in the frequency of electrical impulse generation in the sinus node and slowing of its conduction in the heart, which could ultimately slow the heart rate or terminate tachyarrhythmia. Although there are many ways to achieve this, currently, only a few have a clinical impact. Due to safety issues, some of them lost their clinical potential. The oculocardiac reflex (also known as the trigeminovagal reflex), which is a consequence of bilateral eyeball compression, is no longer used. The complications of reflex are arrhythmogenic adverse effects (asystole, cardiac arrest) and noncardiac consequences, as vagal activation effects include hypotensive episodes, syncope, and gastrointestinal responses such as nausea and vomiting [2]. As well carotid massage carries a risk of neurological complications in first-time seen patients with unknown status of carotid arteries [3]. Another way to augment vagal tone is cold water immersion of the face. Although the high potential for bradycardia, a container with cold water or an extra device (a plastic bag with ice water) is necessary to execute this maneuver. However, its usefulness is limited in an emergency setting. The most popular maneuver used in recent years is the Valsalva Maneuver (VM) and its various modifications [4]. The VM bradycardic response is mediated mainly by the aortic baroreceptor reflex arc. Mechanoreceptors activate the afferent C fibers of the vagal nerve when pressure is applied to the aortic sinus and aortic arch walls. The stimulation of sensory impulses causes the activation of neurons located in the nucleus tractus solitarius (NTS). Bradycardia is the result of the inhibition of neurons in the caudal ventrolateral medulla, leading to a decrease in sympathetic nervous system activation [5].

The Valsalva Maneuver

In 1704, the Valsalva Maneuver was first described in "*De aure humana tractatus*" by Antonio Mario Valsalva as forced expiration against resistance-closed airways [6–8]. VM is still a valuable diagnostic and therapeutic tool. Changes in heart rate and blood pressure are consequences of alterations in intrathoracic and intraabdominal pressures during strain. They are strictly connected with the activation or inhibition of the vagal nerves and are mediated by impulses from the baroreceptors. Therefore, this maneuver is a part of the Ewing battery used to assess autonomic nervous system (ANS) function (sympathetic and parasympathetic components) and baroreflex sensitivity [9]. The VM can be used as a diagnostic tool in cardiology. In patients with heart failure, impaired ventricular function leads to abnormal blood pressure overshoot in response to VM [10, 11]. Due to the reduction in end-diastolic volume, it can

be useful during the differential diagnosis of murmurs. It allows distinguishing sounds developed from aortic stenosis (reduced intensity) from hypertrophic obstructive cardiomyopathy sounds (increased intensity) [12]. Moreover, as mentioned above, bedside VM is still the first choice vagal tone maneuver used for the cessation of paroxysmal supraventricular tachycardia. In addition to its usefulness in cardiology, it is also performed as a part of laryngological examinations, thus allowing a physician to examine an open Eustachian tube or even used therapeutically to stabilize middle ear pressure [6, 13, 14].

In previous studies, many different ways to perform VM have been described. The variations usually concern the position of a patient during maneuvering — the most frequently mentioned ones are sitting, standing, or supine [15]. Another difference refers to the duration of the procedure; some physicians suggest 10 s of exhalation, others suggest 15 s, and others suggest exhalation until exhaustion (i.e., as long as the patient or participant can). Research has consistently shown that the pressure generated during the VM exhalation should be 40 mmHg. However, the presence or absence of forced inspiration just before the trial is still debatable. The efficiency in restoring sinus rhythm in a clinical setting varies between 20% [16] for standard VM and 46% using REVERT study modification [17]. Recently, the Reverse Valsalva Maneuver was revealed to be more efficient and more effortless to teach and perform. Moreover, it does not require any devices to be performed [10, 13, 16–20].

The physiological course of the Valsalva Maneuver

The response to the Valsalva Maneuver is usually divided into 4 phases based on the part of the procedure: the onset of exhalation, strain, release, and recovery. However, during the second phase, it is necessary to distinguish the early and late components, further named phases IIa and IIb, respectively, to evaluate the value of BP decrease. In each phase, characteristic changes in blood pressure and heart rate are observed. Looga *et al.* suggested that in all phases of the VM, we can distinguish early and late subphases. The early subphase is the effect of the primary mechanical disturbance of arterial blood pressure by respiratory changes in intrathoracic pressure, and the subsequent late subphase is the reflex compensatory response to such disturbance [12]. This maneuver provides an excellent test of the integrity of both arterial and cardiopulmonary baroreflex arcs, which activate ANS reflexes during the forced exhalation, strain, and recovery phases. However, phase 0 is often highlighted, which is represented by forced inhalation just before the beginning of the VM [9, 21]. The following changes are responsible for the hemodynamic effects during the Valsalva Maneuver. First, there are changes in intrathoracic pressure and its direct influence on large vessels. Second, changes in venous return influence the filling of the atriums by defining preload. Finally, the most noticeable effects include arterial baroreceptor

activation. Additionally, other factors can influence blood flow during a procedure, such as direct reflexes from cardiac walls and great veins. Looga *et al.* [22] suggested that positive pressure inflation of a lung lobe can activate slowly adapting pulmonary stretch receptors, resulting in a vagal depressor response (bradycardia, peripheral vasodilation, and arterial hypotension). It may be crucial to fully understand the changes taking place in response to VM and, consequently, to adequately use this method to slow down the heart rate [9, 12, 22, 23].

Phase 0 — Deep inspiration

The VM is usually preceded by a deep inspiration. This part is not a compulsory component of the procedure, but it is highlighted in many publications — usually named phase 0. The main changes occurring during inhalation are a result of decreasing intrathoracic pressure followed by an increase in venous return. Initially, a small decrease in blood pressure (BP) is noticed as a result of the redistribution of blood into the lung vessels. Furthermore, a slight heart rate acceleration (HR) is visible as a direct response to inhalation. At the end of this phase, a response from arterial baroreceptors causes a minor increase in blood pressure [9, 12, 23].

Phase I — The early strain

The beginning of forced exhale marks the onset of phase I (lasting 2–3 sec). A sudden increase in intrathoracic and intrabdominal pressures causes direct mechanical compression of the aorta with the ejection of blood peripherally. This results in a transient rise in blood pressure. The increase in blood pressure sensed by aortic baroreceptors leads to the compensation response (reduction in heart rate immediately after the onset straining) modulated by the parasympathetic autonomic nervous system (Fig. 1) [9, 24].

Phase II — The continuation of strain

In this phase, a fall and later partial recovery of arterial pressure and a gradual increase in heart rate during the period of straining are observed. It is divided based on hemodynamic changes into two different subphases. It is impossible to distinguish a proper time to set a strict border between them. The first part is called phase IIa and refers to early blood flow alterations. Then, phase IIb describes all further changes until the end of the strain.

In phase I, increased intrathoracic pressure is accompanied by increased abdominal pressure, causing a direct mechanical shift of the blood into the large veins and the heart's chambers. However, during phase IIa, sustained increased pressure impedes further flow in vessels within the thorax cavity, obstructing venous return. The decreased filling of atriums leads to a significant drop in stroke volume and a further

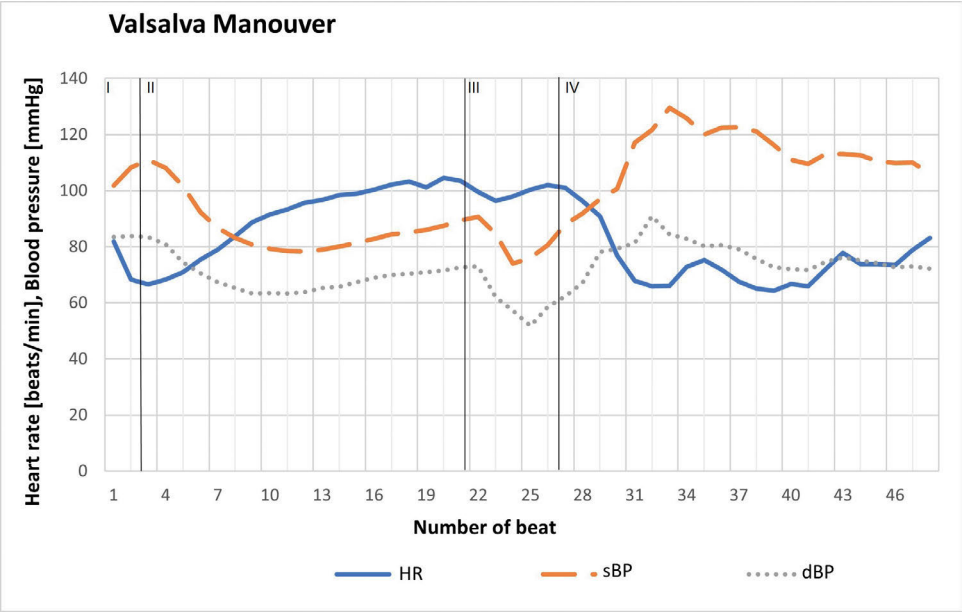

Fig. 1. The cardiovascular hemodynamic changes in response to the Valsalva Maneuver — original recording of an investigated subject. HR — heart rate, sBP — systolic blood pressure, dBP — diastolic blood pressure.

decrease in blood pressure. A considerable decrease in blood flow in the aorta activates the baroreceptor reflex [9]. Its activation leads to the spite in heart rate caused by a withdrawal of cardiovagal influence at the beginning of phase IIb. The increase in peripheral resistance as a result of efferent sympathetic discharge to the vascular muscles and an increase in plasma epinephrine concentration cause the fall in BP to be arrested. As a result of the peripheral resistance increase, despite the still decreased stroke volume, the blood pressure gradually increases [25, 26].

Phase III — The end of the strain

The stop of the strain causes the abrupt release of sustained pressure and fall of intrathoracic pressure. The large vessels inside the thorax are no longer compressed by external forces, and their increased lumen needs to be refilled by blood. The latter causes part of cardiac output to replenish the amount of blood in pulmonary vessels at the reduction of blood pressure, increasing afterload and decreasing stroke volume. Additionally, the peripheral venous reservoir is activated, and the venous return is increasing, thus helping to replenish the lowered stroke volume.

The sudden drop in blood pressure (lasting 1–2 sec) causes a further increase in sympathetic activation mediated by arterial baroreceptors, regardless of its domination starting in phase IIb. As a result, blood pressure and heart rate gradually

rise, often above the starting value. The increase in HR during this phase is not always relevant [24, 27].

Phase IV — The recovery phase

The last part of the Valsalva Maneuver is the time just after the whole procedure. There is a terminal elevation of arterial pressure above control levels and a slowing of heart rate. Usually, it is called the recovery phase and lasts for 20 seconds just after the strain. The beginning of this phase is the result of the mechanisms that started in phase III. Increasing venous return and high peripheral resistance due to circulating mediators of sympathetic activity results in elevated blood pressure. This elevation of blood pressure is sensed by arterial baroreceptors and starts proper recovery, i.e., parasympathetic activation. The most notable changes are visible in the rapid decrease in heart rate, while the elevated blood pressure slowly decreases to baseline levels. Some authors suggest that a more extended period of recovery can occur based on the pressure applied during exhalation on pulmonary vessels [27].

During this phase, the lowest heart rate value in comparison to the highest HR in phase II or III (Valsalva ratio) is used to evaluate the proper response of the vagal nerve. Parasympathetic activation physiologically proceeds to the level of the drop of HR to values significantly lower than the input ones. This vagal response in the Valsalva Maneuver is the theoretical basis of its utility in the cessation of paroxysmal supraventricular tachycardia. Furthermore, recovery of blood pressure causes stabilization of the heart rate and its recovery to the values from the beginning of the procedure [28].

The Reverse Valsalva

The Reverse Valsalva maneuver was primarily described in a series of cases performed in the accident and emergency department by Gaudart *et al.* [19]. This procedure successfully ceases paroxysmal supraventricular tachycardia after Valsalva Maneuver failure [19]. There is no detailed description of this maneuver in previous studies; therefore, we examined the potential physiological mechanisms responsible for cardiovascular hemodynamic changes.

The proposed physiological course of Reverse Valsalva

Phase I — The deep breath

The beginning of deep inhalation with closed airways causes a decrease in intrathoracic pressure, which facilitates the filling of pulmonary vessels. The redistribution of blood decreases the blood volume returned to the atria — the heart's preload fall,

leading to a BP decrease in systemic arteries. The heart rate increases as a response to sympathetic activation. The entirety of phase I is short, lasting only a few beats.

Phase II — The Strain

Phase II represents strain during forced inhalation with the closed glottis. The activated sympathetic nervous system increases the resistance in vessels as well as increased HR from the end of phase I, causing BP to rise. Inhalation against resistance leads to an increase in intrathoracic pressure. Decreased inflow into the left atrium causes contraction of the poorly filled ventricle and mediates the activation of vagal nerve C fibers, causing the Bezold-Jarisch reflex (BJR). This phenomenon decreases peripheral resistance and slows heart rate by activating the nucleus tractus solitaris, which is a depressor center of the central nervous system (CNS) [29]. As a result, we expected decreases in HR and BP. However, the BP decrease in our investigated subject was rather slow (Fig. 2 and 3) [30]. Lowered flow in main arteries decreases afferent impulsation from the carotid and aortic baroreceptors. The decreased impulsation in the NTS promotes the activation of the sympathetic compound of the autonomic nervous system. BJR and baroreceptor afferent stimulation arrive in the same CNS center [29]. The effect of ambiguous stimulation of the NTS is represented by a sustained level of HR and decreasing BP values. Over time, the resistance of

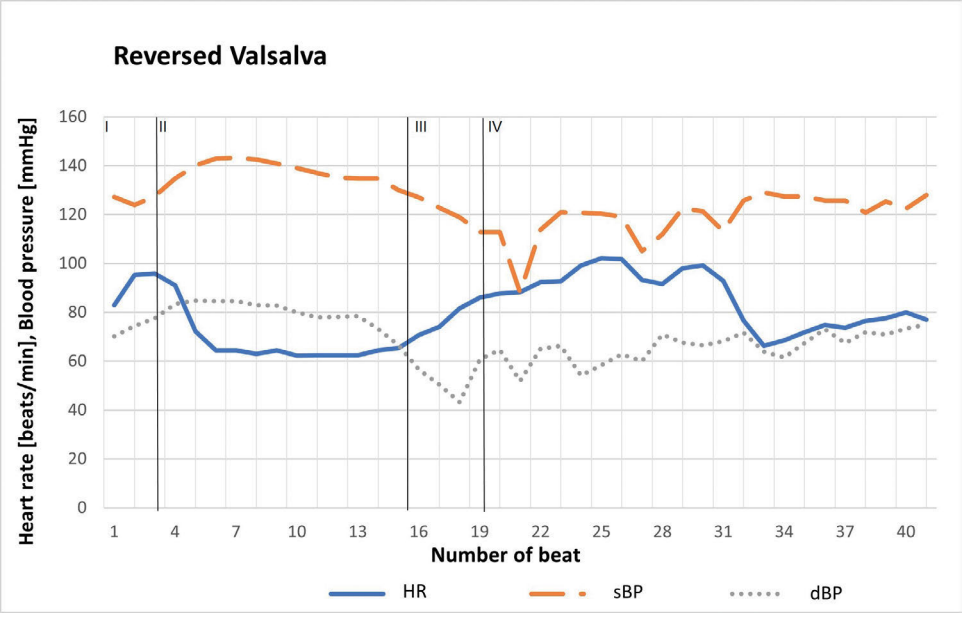

Fig. 2. The cardiovascular hemodynamic changes in response to the Reverse Valsalva Maneuver — original recording from the investigated subject. HR — heart rate, sBP — systolic blood pressure, dBP — diastolic blood pressure.

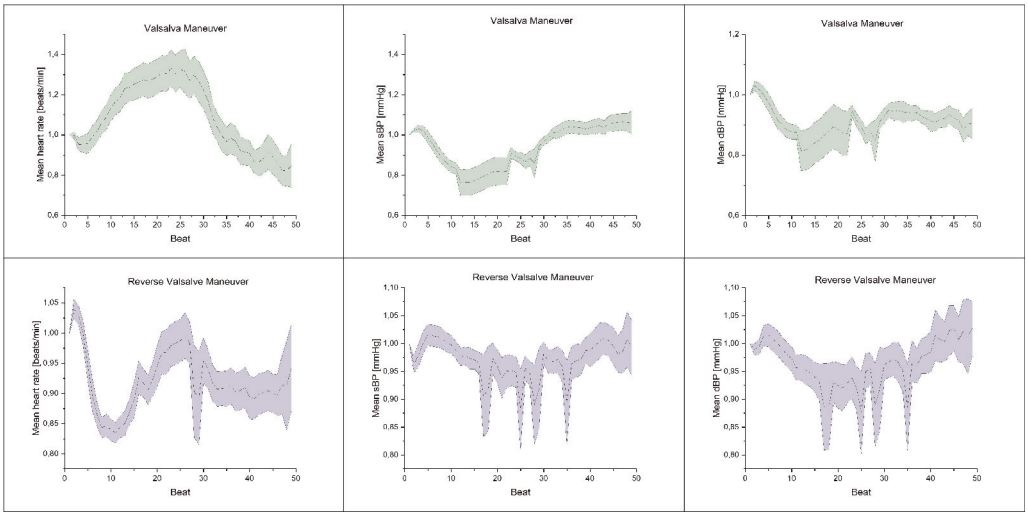

Fig. 3. The graphic view of cumulative proceedings during Valsalva Maneuver and Reverse Valsalva. HR — heart rate, sBP — systolic blood pressure, dBP — diastolic blood pressure.

pulmonary vessels increases, which improves the filling of heart chambers and lowers activation from BJR, leading to an increase in HR. The effect on the BP is shifted over time, but it still decreases in phase II. The effect on BP is inhibited by the previously lowered peripheral resistance [5, 31].

Phase III — The end of the strain

Forced exhalation causes a transient drop in blood pressure and an accelerating heart rate. In the individual subject, the change in HR value is unnoticeable (Fig. 2). These effects are better highlighted in cumulative records (Fig. 3). The increasing trends in BP and HR are sustained. BP increases gradually and less dynamically with an increase in peripheral resistance.

Phase IV — Recovery

During this phase, a further tendency to increase HR and BP was observed. In the phase of recovery, the values of BP and HR are not stable. The levels of BP and HR are interrupted by transient increases and decreases, likely caused by the dysregulation of the breathing pattern. Subsequent inhales and exhales are prolonged. The increase in BP can irritate mechanoreceptors in the arterial wall. Further activation of baroreceptors activates the NTS, causing inhibition of the sympathetic nervous system (compensatory bradycardia) and lowering of the previously increased peripheral resistance. The latter changes lead to the stabilization of the BP parameters into input values. Furthermore, the HR stabilizes as well. This leads to increased tension in the aortic

arch and a decrease in baroreceptor activation, which is represented by lowering the HR. The recovery effect on BP level is delayed because of previous increased peripheral resistance.

The aims of the study

Despite the fact that multiple scientific reports have described VM, none of them have compared its cardiovascular hemodynamic effect to that of the RV. This study aimed to distinguish the differences between two vagal maneuvers: the standard VM and the novel RV. The research compared hemodynamic changes occurring during these procedures. Continuously recorded blood pressure (BP) and heart rate (HR) allowed us to indirectly evaluate vagal tone augmentation during classic and reverse maneuvers. Additionally, autonomic system activity based on frequency-domain heart rate variability (HRV) analysis was performed to compare changes occurring during the VM and RV. Moreover, with a beat-to-beat analysis of HR and BP, it was possible to track the course of these procedures. Finally, the process of executing these different maneuvers was evaluated.

Material and Methods

Participants

Investigated participants: The study included 15 healthy persons, including 12 females and 3 males, with a mean age of 24.73 (± 2.81) years. The inclusion criteria were as follows healthy young adults (aged 18–29). The standard exclusion criteria for ANS examinations were applied: diabetes mellitus, obesity (BMI >30), cardiovascular diseases (hypertension, coronary artery disease, valvular heart disease, cardiac arrhythmias), neurological diseases, or the use of medication that may modulate cardiovascular or autonomic nervous system function [32].

Methods

The procedures were performed in the afternoon in a quiet, relaxed atmosphere. Careful instruction about the performance of the tests were provided to patients before the study. Controlling for the time and place allowed us to minimize any external stimuli that could affect the results of the study. All of the records were performed by the same physician in the same order to ensure similar conditions for every volunteer. During the visit, the investigator took a brief medical history of the patient and obtained a 10-min record of cardiovascular hemodynamic parameters at rest. The protocol of the pre-examination preparation was similar to that described our previous study [32]. The limb ECG, continuous beat-to-beat blood pressure (BP),

and oscillometric BP were recorded using the Task Force Monitor 3040i (CNSystems, Graz, Austria). The entire procedure was performed noninvasively. The frequency-domain HRV analysis was performed using Task Force Monitor software V2.2.

The VM and RV were performed three times during one investigation. Each attempt was executed in the same way. The physician described the entire procedure to the patients, and the patients confirmed their comprehension. The subjects were investigated in a sitting position with continuous beat-to-beat noninvasive measurements of blood pressure and ECG monitoring before, during, and after the procedure. We decided to perform the classic VM because the RV was described only in the sitting position [19]. Additionally, we used the simplest method rather than using the various modifications to minimize the differences of performance between the 2 maneuvers.

VM protocol

On arranged signal, deep inhalation was performed. The investigated subject blew into a mouthpiece of the manometer to maintain 40 mmHg pressure for 15 sec. The measurement was taken just after the whole procedure for the next 20 s to obtain data during recovery. The investigator held the manometer to sustain proper pressure for the given time and controlled the maneuver time. Between tries, the participant rested for 5 min. This break duration was sufficient to normalize HR and BP values.

RV protocol

In a sitting position, after a normal exhalation, the patient was attempting to inhale against resistance with a closed mouth and pinched nose for 10 s [19]. The monitoring of systolic and diastolic BP and HR was continued for 25 s after the trial to receive the same record time as during the VM (35 s). This maneuver was also performed 3 times with appropriate breaks between consecutive tries.

Heart rate variability (HRV)

HRV analysis is one of the most popular tools for evaluating the autonomic nervous system (ANS) in humans. The frequency-domain HRV analysis differentiates the influences of sympathetic and parasympathetic activation on cardiovascular system function [33]. The frequency-domain analysis of the RR intervals was based on the adaptive autoregressive parameter (AAR) algorithm. The frequency-domain HRV analysis includes LF (component of the low-frequency domain; 0.04–0.15 Hz; modulated by both the sympathetic and parasympathetic nervous system and associated with baroreceptor activity), HF (component of the high-frequency domain; 0.15–0.4 Hz, modulated by the parasympathetic nervous system, connected with respiration

and blood pressure changes), and total power (TP). In this study, we decided to calculate the differences in HRV parameters since the same participant was under examination with two different maneuvers.

Data analysis and visual presentation response to RV and VM tests

The analysis of the HR changes during the VM and RV is presented in three different ways (Table 2). First, we compared HR values in phase 0 — at the beginning of the individual maneuvers — to the phase with minimal and maximal values. The lowest HR was recorded during phase II of RV and phase IV of the VM, while the highest preexisted in phases just before (phase I during the RV and phase III in VM). This differentiation enabled us to calculate not only the decrease in HR from the beginning to the lowest point but also the most significant decrease between the extreme following parts.

The measurements obtained in both procedures were analyzed, were chosen to prepare a cumulative chart of maneuvers. Due to differences in HR and BP values at the starting point of the trial, raw data were not analyzed. Parameters measured during the first VM and RV heartbeats were set as a reference for the rest of the record. The relation between the next beats to the first one from a participant was summed up to prepare a visual representation of typical VM and RV from healthy volunteers. The graphs were based on changes in relation to consecutive heartbeats of participants rather than changes in time. This approach can lead to some negative consequences, such as shifts of phases (i.e., the same beat did not represent the same second of record). We decided that such a presentation of data will enable us to calculate the standard deviation of particular measurements. Odd values — artifacts — were brushed out (<2%) based on visual representation. Figures were prepared in TIBCO Statistica for Windows, version 13.3 PL (TIBCO Software Inc., Palo Alto, California, United States; Jagiellonian University license).

Statistical analysis

Statistical analyses and data collection were performed using Predictive Solutions PS IMAGO PRO Academic for Windows, version 8.0 (Predictive Solutions, Kraków, Poland Jagiellonian University license) The visual distribution of histograms was used to verify the normal distribution of variables, and data meeting criteria were presented as the means with SD. The nonnormal data are presented as medians with Q1 and Q3 values. For intergroup comparisons of quantitative variables, the unpaired t test (for normally distributed variables) or the Mann–Whitney test (for nonnormally distributed variables) was used. Correlations between the pairs of HR, BP, and HRV parameters were assessed using the Wilcoxon signed rank test or paired t test, depending on the normality of the distribution. The significance level was set at a P value of less than 0.05.

Ethical approval

The study was approved by the Bioethics Committee of Jagiellonian University in Kraków, Poland (no. of permission, 1072.6120.83.2021). All participants were instructed about the aim of the study, and written consent was obtained before enrollment, in accordance with the Declaration of Helsinki.

Results

Fifteen healthy subjects with a mean age of 24.73 (± 2.81) years (age from 18 to 29) participated in the study. There were 12 females (80%) and 3 males (20%). All participants had normal sinus rhythm in ECG, normal heart rate, and blood pressure within age-appropriate normal parameters. Anthropometric measures such as weight, height, BMI, body surface area (BSA), and basic hemodynamic parameters (HR, BP) were normal (Table 1).

Table 1. Characteristics of the investigated group.

Demographic Data		
Participants (n)		15
Sex (n)	Female	12
	Male	3
Age (years)		24.73 ± 2.81
BMI (kg/m2)		22.18 ± 3.15
BSA (m2)		1.76 ± 0.21
Hemodynamic Parameters at Rest		
Heart Rate (beats/minute)		68.39 ± 8.18
Systolic Blood Pressure (mmHg)		96.78 ± 10.3
Diastolic Blood Pressure (mmHg)		61.76 ± 6.81
Mean Blood pressure (mmHg)		75.89 ± 7.47

Analysis of the simplicity of maneuver execution

Both maneuvers were performed easily without any complications. All three attempts were completed repetitively without any further tips (except a short explanation). During the RV investigation, participants were able to control time on their own, and additional equipment was unnecessary. In contrast to the VM, the subject used

a special device to conduct it with a mouth-peace (20-ml syringe) and manometer. Additionally, simultaneous control of the time and pressure required slight support from the examiner in the VM.

Cardiovascular hemodynamic analysis

In phase 0, HR was similar in both groups (86/min vs. 80/min). A higher HR value was observed during the standard maneuver: for RV, it was 90/min in phase I vs. 111/min in phase III in the VM (p = 0.008). The lowest HR during the RV was noted in phase II, while the lowest HR in the VM occurred in phase IV. The HR value was greater in response to the RV than the VM 70/min vs. 59/min (p <0.001), respectively (Table 2).

Table 2. Heart rate change in particular phases of different vagal tone-enhancing maneuvers.
HR — heart rate; p^A — Mann–Whitney U test; p^B — Wilcoxon signed-rank test, and Δ — differences HR parameters.

Parameters	Reversed Valsalva	Valsalva Maneuver	p
HR — phase	86 (8181; 90.92)	80 (67.04; 89.9)	0.352 [A]
HR — phase of maximal HR	90 (86.18; 100.74)	111 (98.85; 125.94)	**0.008** [A]
HR — phase of minimal HR	70 (61.87; 75.53)	59 (55.31; 62.98)	**<0.001** [A]
Indirect change in heart rate — ratio			
HR 0 to phase of minimal HR ratio	0.81 (0.75; 0.88)	0.79 (0.64; 0.86)	0.27 [A]
HR — phase of the maximal HR to HR in phase 0 — ratio	1.04 (1.03; 1.09)	1.33 (1.22; 1.62)	**<0.001** [A]
HR in the phase of minimal HR to HR in the phase of maximal HR — ratio	0.76 (0.74; 0.86)	0.51 (0.43; 0.66)	**<0.001** [A]
Subgroup analysis — direct change in heart rate			
Δ phase 0 — phase of minimal HR	–16.39 **(p <0.001)** [B]	–15.78 **(p <0.001)** [B]	
Δ phase 0 — phase of maximal HR	+3.66 **(p <0.001)** [B]	+25.7 **(p = 0.001)** [B]	
Δ phase of maximal HR — phase of minimal HR	–21.89 **(p <0.001)** [B]	–55 **(p <0.001)** [B]	

Analysis of the indirect change in HR is represented as the changes in HR between particular phases — expressed as a ratio. The difference between the phase of minimal HR and the HR in phase 0 is similar during the RV and the VM (0.81 vs. 0.79; p = 0.27). The increase in HR from phase 0 to phases of maximal HR was lower during the RV (1.04 vs. 1.33; p <0.001). The highest change in the HR phase of minimal HR to maximal HR showed a less prominent change during the RV (0.76 vs. 0.51; p <0.001) (Table 2).

The analysis of the direct change in HR in subgroups showed that the changes between particular phases of the maneuvers were significant in response to both tests: RV and VM. The direct differences in HR between phase 0 and the minimal HR phase are similar during the RV and VM: decrease of HR by 16.56/min vs. 15.78/min. The increase in HR from phase 0 to the phase of maximal HR was smaller in the RV (3.66/min) than in the VM (25.7/min). The differences between the maximal HR and minimal HR during the test were lower in the RV (21.89/min) than in the VM (55/min) (Table 2).

The graphic view of participants' cumulative courses during the RV and VM

The solid line represents the HR, sBP, and dBP values, while the shadows on the graphs represent confidence intervals. The whole analysis is based on consecutive beats, not on the time, causing shifts of respective phases. This approach is explained in the methods and materials section. The cumulative course of maneuvers performed by participants corresponds with previous reports. A full description based on previous research can be found in the introduction section. In the course of RV, 4 different phases can be distinguished based on the activity of the participant (Fig. 3). Additionally, in the cumulative course of the RV (Fig. 3), we observed similar changes in HR from the 15th to 30th seconds as in the VM (Fig. 2).

Autonomic system activity — HRV analysis

The HRV parameter analysis showed that VLF, LF, HF, and TP before the procedure did not differ significantly between RV and VM. However, the comparison of HRV indices during the most bradycardic phase for RV (phase II) and VM (phase IV) VLF, LF, and TP were significantly higher in VM than during the RV, and only HF indicators were similar between groups (333.24 vs. 331.84 ms^2; $p = 0.491$) (Table 3).

The value of indirect changes in HRV parameters represented the ratio of the level of parameters from the bradycardic phase to during the 10 s before analysis. The LF (1.09 vs. 1.7; $p = 0.02$) and TP (1.03 vs. 1.6; $p = 0.01$) ratios were significantly lower during the RV. The VLF (1 vs. 1.84; $p = 0.07$) and HF (0.98 vs. 1; $p = 0.85$) changes did not differ between maneuvers (Table 3).

The subgroup analysis showed a direct change in the particular HRV frequency domain in both maneuvers. During the RV, none of the HRV indices (VLF, LF, HF, and TP) showed a significant change between the extreme following parts. In contrast, during the VM, significant differences were noted in the VLF, LF, and TP parameters. The direct change in HF was nonsignificant in both subgroups. In the comparison between the two maneuvers, there was a higher increase in VLF, LF, and TP parameters during the VM than during the RV (Table 3).

Table 3. Heart rate variability (HRV) — the frequency domain analysis parameters. The comparison of values before the procedure to phases of lowest HR (plateau).

Parameters	Reversed Valsalva (RV)	Valsalva Maneuver (VM)	p
Analysis of 10 seconds before the procedure			
VLF [ms^2]	543.84 (199.65; 852.42)	840.7 (465.61; 1574.99)	0.06 ^{A}
LF [ms^2]	1018.17 (876.59; 1442.28)	1441.07 (827.87; 1847.95)	0.435 ^{A}
HF [ms^2]	313.81 (230.86; 437.6)	419.52 (274.39; 531.65)	0.312 ^{A}
TP [ms^2]	2043.45 (1369.09; 3288.94)	2805.96 (1643.32; 4082.34)	0.198 ^{A}
Analysis 10 seconds phase II of RV and phase IV of VM			
VLF [ms^2]	548.68 (298.04; 1342.68)	1936 (524.21; 3918.46)	**0.027** ^{A}
LF [ms^2]	1166.28 (902.84; 1699.08)	2242.44 (1429.91; 5942.74)	**0.009** ^{A}
HF [ms^2]	333.24 (202.12; 442.11)	331.84 (287.00; 581.07)	0.491 ^{A}
TP [ms^2]	2467.79 (1534.13; 3690.17)	4498 (2419.81; 10245.68)	**0.012** ^{A}
The indirect change of HRV			
VLF [ms^2]	1 (0.83; 1.93)	1.84 (1.09; 2.74)	0.07 ^{A}
LF [ms^2]	1.09 (0.95; 1.25)	1.7 (1.11; 3.14)	**0.02** ^{A}
HF [ms^2]	0.98 (0.86; 1.05)	1 (0.8; 1.13)	0.85 ^{A}
TP [ms^2]	1.03 (0.98; 1.19)	1.6 (1.11; 2.99)	**0.01** ^{A}
The direct change of HRV			
Δ VLF	+5.7 (p = 0.78) ^{B}	+708.88 **(p = 0.005)** ^{B}	
Δ LF	+113.52 (p = 0.177) ^{B}	+873.39 **(p = 0.004)** ^{B}	
Δ HF	−5.91 (p = 0.88) ^{B}	−1.17 (p = 0.594) ^{B}	
Δ TP	+85.68 (p = 0.064) ^{B}	+1463.82 **(p <0.001)** ^{B}	

p^{A} — U Mann-Whitney test; p^{B} — Wilcoxon signed rank test and Δ — differences HRV parameters.

Discussion

The Valsalva Maneuver is a well-known procedure described and used worldwide in many clinical situations. Many studies have tried to modify the methodology of this vagal maneuver to achieve maximal activation of the ANS. The most common changes regarding length, duration, and posture of the VM test were investigated. To our knowledge, this study is the first comprehensive comparison of the effects of the Valsalva Maneuver and Reverse Valsalva Maneuver based on HR differences and autonomic system activity. This is the first study to fully describe the course of the Reverse Valsalva Maneuver investigated by Gaudart *et al.* to identify the underlying mechanisms [15, 17, 19, 20, 28, 34].

When comparing our procedure with the Valsalva Maneuver, we fulfilled 2 out of the 3 criteria described in the review by Smith *et al.* which presents the gold standard of the VM protocol. We decided to perform it in different positions — i.e., the sitting position, which we used for the RV [28] — to better compare these procedures. Previous studies suggest that the vagal response could be more highlighted in the supine position. The REVERT study suggests that the best clinical efficiency is achieved with passive leg raise by a physician after the Valsalva strain is performed [15]. We decided to perform classic VM with a 15-s duration and 40 mmHg pressure in a sitting position; this was the easiest approach.

The main observation from our research is that during the VM, changes in HR and activation of the autonomic nervous system (an increase in VLF, LF, TP) are greater than during the RV. The higher decrease in HR during phase IV of the VM is likely due to higher activation of the sympathetic nervous system in phase II as a response to the decrease in blood pressure. This confirmed the increases in HRV parameters (VLF, LF, and TP). Additionally, in phase VI of the VM, we can observe antagonistic influences from two sets of receptors; for these reasons, a bradycardic response appears in place of tachycardia, although peripheral vasoconstriction still continues. This is a consequence of weak stimulation of baroreceptors (due to low strain pressure) with the concomitant vagotonic state of autonomic activity [22]. Our study investigated healthy volunteers with normal cardiovascular ANS regulation. The correct reflex from the baroreceptors determines such an effect. During paroxysmal supraventricular tachycardia, sympathetic activity is increased, probably as a result of "downregulation" of adrenergic receptors, and the additional activation of the sympathetic ANS in response to VM (II phase) will be lower than in healthy subjects. For this reason, the effect of vagal influence in phase IV of the VM will be lower than that during the RV [9, 35].

In our study, the reverse Valsalva protocol was used as in the Gaudart *et al.* investigation [19]. The procedure itself was described very strictly. However, because of the lack of sufficient data in previous studies, we did not know what the recovery time should be when significant hemodynamic changes occur. Because our investigation aimed to compare the VM and RV, we decided to record them for the same duration: up to 35 s from the beginning in a sitting position [19].

The individual graphs of HR and systolic and diastolic BP showed four clear phases in the VM and RV that were dependent on respiratory changes in intrathoracic pressure (Fig. 1 and 2). The cumulative graphic visualization of the proceedings in VM and RV showed that the whole course of the VM was similar to the results of the previous investigation (Fig. 3). Unfortunately, the small group of participants taking part in our study influenced the course with some artifacts, mainly affecting the dBP record [8, 12, 13].

In contrast to Gaudart *et al.* [19], who based explanations of physiological changes during the RV maneuver on the Toynbee maneuver, Zöllei and Rudas suggested that the RV is not a reversed vagal maneuver but is rather an uncalibrated well-known Muller Maneuver (MM) described by Morgan *et al.* [36, 37]. We agree in the nomenclature that both the RV and MM cause mainly parasympathetic activation by the cranial X nerve and thus should be called vagal maneuvers instead of reversed maneuvers. However, we found some discrepancies in the hemodynamic changes during our study and the Morgan *et al.* study [19, 36, 38, 39].

Their study showed MM based on 20 seconds of forced inspiration against the closed glottis with a pressure of 40 mmHg. They observed a decrease in BP during the first 10 s of the trial and an increase in HR with lowered sympathetic nerve activity. Furthermore, after 10 s, the parameters stabilize, and then BP and sympathetic nerve activity increase, even exceeding the input value during recovery time, while HR decreases. They explained the changes simply by the effect of negative intrathoracic pressure accompanied by sympathetic inhibition with further sympathetic activation after pressure release. However, during our study, we observed a simultaneous decrease in HR and BP that did not completely fit the underlying pathomechanism proposed by Morgan *et al.* The cardiovascular hemodynamic pattern in our study was better described as BJR [29, 36]. The BJR phenomenon decreases peripheral resistance and slows the heart rate by activating the NTS in the depressor center of the CNS [29].

The RV and MM are complicated maneuvers, and further investigation needs to be performed. Similar to the VM, the pattern of hemodynamic response to forced expiration against the closed glottis may not be identical across all subjects.

Limitations of the study

Our study has potential limitations. First, the study included a small sample size of only 15 participants. This small sample size influences the power of the statistical tests; additionally, a larger sample would enable us to divide participants into subgroups based on the input heart rate. Such an approach could enhance our understanding of the changes in cardiovascular hemodynamic parameters during the Reverse Valsalva and improve the comparison of the two different maneuvers.

According to the guidelines, the analysis of HRV parameters should be based on longer ECG records. For the HF band (0.15–0.40 Hz) analysis components are typically recorded over a minimum of 1 min [40], but for the LF band (0.04–0.15 Hz), the parameters are recorded for a minimum of 2 min [33]. Maneuvers performed in our study were persistent for less than one minute, so a longer measurement period would be pointless. Because parasympathetic nerves exert their effects more rapidly (<1 s) than sympathetic nerves (>5 s), they can produce contradictory actions, such as

speeding and slowing the heart; therefore, their effect on an organ depends on its current balance of ANS activity [41]. It is important to measure the ANS in VM and RV maneuvers because changes in AS activity occur in response to tests.

All of our measurements were performed in a specially prepared ANS laboratory. Moreover, our participants were healthy and young, and they did not have any important medical history or treatment. Many factors, such as comorbidities and drugs, can influence the impact on the autonomic nervous system. For this reason, regardless of the increase in parasympathetic tone during both maneuvers in our study, the ability to cease paroxysmal supraventricular tachycardia may be different in patients. Therefore, it did not perfectly reflect the clinical situation. Future results should be studied in the clinical setting during RCT. Moreover, the vagal effect of RV should also be compared to VM performed in a supine position or even with the procedure shown in the REVERT study [15].

Conclusion

The Valsalva Maneuver and the Reverse Valsalva Maneuver have a similar effect on the slowing of HR in comparison to the beginning of the procedure. However, an analysis of maximal differences in heart rate showed more significant changes during the VM. The changes in HRV parameters during both procedures in particular phases of RV and VM suggest that the autonomic nervous system is activated alternately, so these tests can be used complementarily in a clinical setting with different results. Additionally, a comparison of the visual presentation of cardiovascular hemodynamic changes suggests that the method of achieving a decrease in heart rate differs based on underlying mechanisms. This can be crucial in the clinical setting for the cessation of paroxysmal supraventricular tachycardia. It appears that both maneuvers can be used not only equivalently but even complementarily.

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Author contributions

All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by A.B., M.J., K.A., and A.F. The first draft of the manuscript was written by A.B., and all authors commented on previous versions of the manuscript. All authors reviewed and approved the final manuscript.

Conflict of interest

None declared.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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