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Autonomic function testing: Compliance and consequences

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ABSTRACT

Background: The deep breathing test (DB) and Valsalva maneuver (VM) are used to detect autonomic dysfunction. The VM induces sympathetically mediated changes in blood pressure (phase II late, phase IV, and recovery time) and both tests induce vagally mediated heart rate changes. There is limited information on effects of key variables, compliance with testing and the effects of non-compliance This study has twin goals of evaluating compliance with standard instructions and the effects of changes in key variables. We also evaluated the effect of position on the VM.

Material and methods: Forty healthy males performed DB at air exchange volumes of 50, 80, and 100% of vital lung capacity (VLC). The VM was performed at 40 and 30 mm Hg expiratory pressure for 15 and 10 s in sitting and supine position, respectively.

Results: Participants performed DB at lower volumes than intended and were not able to maintain 100% VLC for the duration of the test. The DB heart rate response decreased 6.3 beats/min per liter below VLC. During the VM, subjects blew at lower pressures than instructed. The VM responses were significantly larger with longer expiration durations, higher expiratory pressures and when performed sitting. Performing the VM at 40 mm Hg for 10 s in supine position increased the odds ratio of experiencing flat-top responses.

Conclusion: The ability of subjects to strictly comply with methodological guidelines significantly improves results. Recording of both test parameters and ensuing results is suggested.

1. Introduction

The deep breathing (DB) test and Valsalva maneuver (VM) are key methods for the assessment of the autonomic nervous system and are commonly used for the diagnosis of cardiovascular vagal and adrenergic dysfunction (Freeman and Chapleau, 2013; Low, 2003; Novak, 2011). Although methodology has been standardized, there is considerable variability in its application. This study focuses on 2 key questions of compliance with standard methodology and the consequences of lack of compliance. To sharpen the study, we continuously monitored test parameters of both lung volumes (for DB) and expiratory pressure (for VM). We also compared the standard supine position with VM with the subject sitting up.

The DB test consists of forced maximal respiration, at a frequency of 6 cycles/min, alternating between forced maximal inhalation and exhalation in a steady airflow. During the DB test, the heart rate (HR) increases during inspiration and decreases during expiration. HR changes to deep breathing have a high specificity for detecting cardiovagal dysfunction with both vagal nerve afferents and efferents mediating the response (Wheeler and Watkins, 1973).

The VM consists of a forced expiration against a resistance of 40 mm Hg, for 15 s. During this period, cardiovascular changes are used as indirect measurements of the autonomic nervous system function. The ratio between minimal and maximal R-R interval (during and after strain, respectively) is called the Valsalva ratio (VR), mediated through both vagal inhibition and increased sympathetic activation (Rothschild et al., 1987). The adrenergic activity is measured through changes in blood pressure (BP).

The BP undergoes four distinct phases during the VM. Phase I consists of a transient rise in BP from mechanical compression of major blood vessels induced by the straining (Fig. 1).

This leads to a drop in BP due to reduced venous return, called

Abbreviations: VM, Valsalva maneuver; DB, deep breathing test; BP, blood pressure; PRT, pressure recovery time; P_II_E, phase II early; P_II_L, phase II late; P_IV, phase IV; VR, Valsalva ratio

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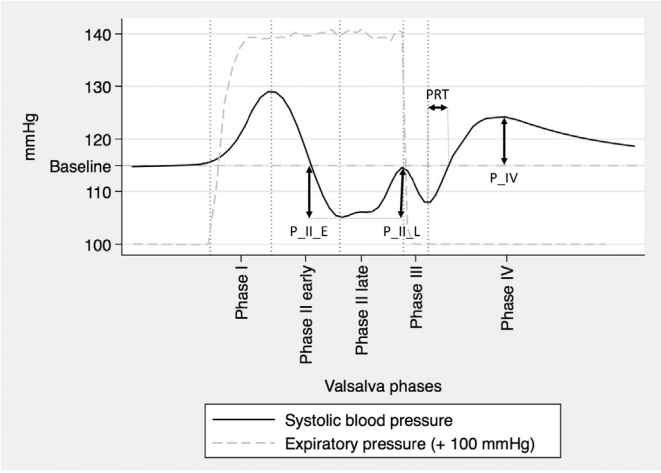

Fig. 1. A normal blood pressure (BP) response to the Valsalva maneuver (VM). The rise in BP in phase I is due to the mechanical straining during expiration. The decrease in BP during phase II early is due to decreased venous return. The BP rise during phase II late is due to increased cardiovascular adrenergic activity increasing cardiac output. The BP drop in phase III is due to the mechanical release of straining. The BP rise in phase IV is due to the persistent increased adrenergic activity induced by the VM. Phase IV lasts until the BP reaches the baseline value.
The measured variables of the Valsalva maneuver. P_II_E is measured as the difference between the baseline BP and the lowest BP during phase II of the VM. P_II_L is measured as the difference in BP between the lowest BP during phase II and the largest succeeding BP in phase II of the VM. PRT is calculated as the duration from the lowest BP in phase III of the VM until the baseline BP is reached. P_IV is measured as the largest positive difference in BP from baseline during phase IV. Phase IV lasts until the BP reaches baseline.

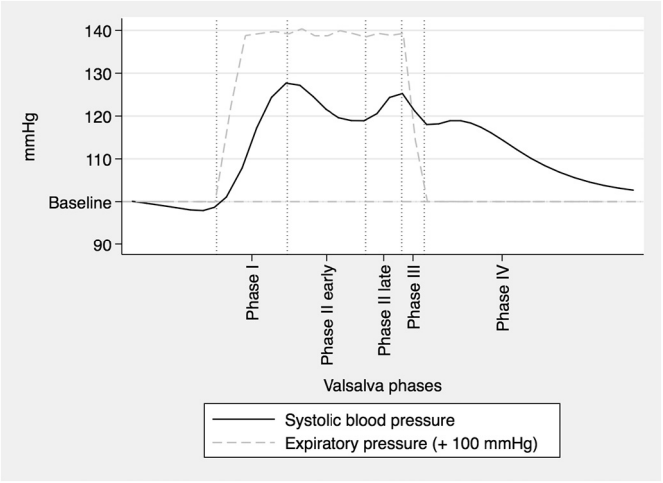

Fig. 2. A flat-top response to the Valsalva maneuver. Note that the blood pressure does not descend below the baseline value during phase II.

phase II early. The BP drop induces baroreceptor unloading and increase in adrenergic activity with a subsequent increase in BP called phase II late. At the release of the expiratory straining, the BP drops during phase III due to a sudden release of the increased intrathoracic pressure. After the release, the BP returns to and exceeds the baseline BP value as phase IV due to both increased cardiac venous return and continued increased adrenergic activity (Denq et al., 1998; Looga, 2005; Wada et al., 2014). The duration from phase III until the BP reaches baseline BP value is measured as the pressure recovery time (PRT) (Fig. 1).

Despite the apparent simplicity of the VM, the BP response does not always follow the typical four phasic pattern (Low, 2008). If the VM is inadequately performed, the intrathoracic pressure may not be sufficient to inhibit venous return and decrease cardiac preload. In such event, the BP during phase II early will not descend below baseline BP, also known as a “flat-top” or “square wave” response (Fig. 2), and sufficient unloading of arterial baroreceptors is thus not achieved.

Methodology for these studies have been standardized and are widely used in both clinical and research settings, (Sharabi et al., 2003; Svigelj et al., 2015) but despite this, there is still significant variance and compliance across studies (Pal et al., 2013; Tonhajzerova et al., 2009). Currently, very few measures are monitored to ensure sufficient methodological compliance.

Earlier studies have investigated the effect of varying pressure and duration of expiration and subject positioning during the VM (Benarroch et al., 1991; Smith et al., 1996; Ten Harkel et al., 1990); however, the actual expiratory parameters are typically not recorded and considered in the statistical analysis. For DB, the tidal volumes ventilated and the breathing patterns are typically not recorded, although lower tidal volumes have shown decreased HR responses (Brown et al., 1993; Hirsch and Bishop, 1981).

For the DB test, we wanted to examine the actual amount of air ventilated, when instructed to breath at maximal respiratory volume, and the influence on the DB test response at different air volumes. We hypothesized that the participants performed the DB test at lower tidal volumes than instructed, resulting in reduced DB HR responses. For the VM, we examined the cardiovascular adrenergic responses and HR changes during variations in expiratory pressure between 30 and 40 mm Hg, changes in duration of pressure from 10 to 15 s and supine versus sitting position. Moreover, we wished to investigate if these test parameters influenced the risk of experiencing flat-top and no phase II late responses. We hypothesized that the likelihood of a normal autonomic response increases with increased effort regarding time and pressure and in sitting position.

2. Methods

2.1. Participants

Forty healthy male volunteers (mean age ± SD; 23.5 ± 2.5 years) were recruited through advertising at Aarhus University and Aarhus University Hospital. Exclusion criteria were age < 18 years, abnormal 12-lead electrocardiogram, any known cardiovascular or neurological disease, hypertension, diabetes, malignancy, alcoholism, substance abuse, or regular use of medicine of any kind.

2.2. Procedure

The study was carried out during a 5-month period from January to May 2015 according to the Helsinki Declaration and was approved by the local ethics committee (project-ID: M-2014-336-14), Viborg, Denmark, and the Danish Data Protection Agency. The experiment was registered at Clinicaltrials.gov (ID: NCT02397681). All participants received written and oral information about the study prior to inclusion and gave their written informed consent upon entering the study.

2.3. Experimental setup

The experiment included two sessions on 2 separate days (days interval ± SD, 16 ± 11 days) at the Danish Pain Research Center, Aarhus University Hospital, Denmark.

At the first session, the medical history was obtained and a physical examination was performed. If the medical screening was normal, participants received instructions in the execution of DB and the VM and practiced these until sufficiently executed. Vital lung capacity (VLC) was measured.

At the second day, the participants were tested between the hours of 8:00 to 15:00 in a quiet room, with a room temperature of 23.1 °C (SD ± 0.6 °C). Participants were not allowed to receive pharmacological treatment 48 h prior to the testing and had to abstain from strenuous exercise for at least 24 h and from alcohol, caffeine, and