

## REVIEW

# The Valsalva manoeuvre: physiology and clinical examples

L. Pstras,<sup>1</sup> K. Thomaseth,<sup>2</sup> J. Waniewski,<sup>1</sup> I. Balzani<sup>3</sup> and F. Bellavere<sup>4</sup>

<sup>1</sup> Institute of Biocybernetics and Biomedical Engineering, Polish Academy of Sciences, Warsaw, Poland

<sup>2</sup> Institute of Electronics, Computer and Telecommunication Engineering, National Research Council, Padua, Italy

<sup>3</sup> Department of Medicine, Sant'Antonio Hospital, Padua, Italy

<sup>4</sup> Provincial Agency for Health Services (APSS), Trento, Italy

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Correspondence: L. Pstras,  
Institute of Biocybernetics and  
Biomedical Engineering, Polish  
Academy of Sciences, Ks.  
Trojdena 4, 02-109 Warsaw,  
Poland.  
E-mail: leszek.pstras@ibib.waw.pl

## Abstract

The Valsalva manoeuvre (VM), a forced expiratory effort against a closed airway, has a wide range of applications in several medical disciplines, including diagnosing heart problems or autonomic nervous system deficiencies. The changes of the intrathoracic and intra-abdominal pressure associated with the manoeuvre result in a complex cardiovascular response with a concomitant action of several regulatory mechanisms. As the main aim of the reflex mechanisms is to control the arterial blood pressure (BP), their action is based primarily on signals from baroreceptors, although they also reflect the activity of pulmonary stretch receptors and, to a lower degree, chemoreceptors, with different mechanisms acting either in synergism or in antagonism depending on the phase of the manoeuvre. A variety of abnormal responses to the VM can be seen in patients with different conditions. Based on the arterial BP and heart rate changes during and after the manoeuvre several dysfunctions can be hence diagnosed or confirmed. The nature of the cardiovascular response to the manoeuvre depends, however, not only on the shape of the cardiovascular system and the autonomic function of the given patient, but also on a number of technical factors related to the execution of the manoeuvre including the duration and level of strain, the body position or breathing pattern. This review of the literature provides a comprehensive analysis of the physiology and pathophysiology of the VM and an overview of its applications. A number of clinical examples of normal and abnormal haemodynamic response to the manoeuvre have been also provided.

**Keywords** autonomic function, baroreflex, blood pressure, cardiovascular homeostasis, haemodynamics, heart rate variations.

The original Valsalva manoeuvre (VM) was popularized and described in detail by an Italian anatomist, physician and surgeon Mario Antonio Valsalva (1666–1723) in his work 'De Aure Humana Tractatus' (Treatise on the Human Ear) in 1704, although, allegedly, it was already used by Arab physicians back in 11th century (Canalis 1990). The manoeuvre consists of a voluntary forced expiratory effort against a closed airway (e.g. closed mouth and nose) and is

used traditionally in otolaryngology for testing the openness of the Eustachian tubes and expelling pus or foreign bodies from the middle ear (Editorial, 1970).

Despite its seeming simplicity, the manoeuvre can result in complex transient cardiovascular and neuro-hormonal alterations associated with the increased intrathoracic and intra-abdominal pressure and the corresponding changes in blood pressure (BP). Therefore, it is also often used in cardiology as a relatively

simple, inexpensive, non-invasive and reproducible method to diagnose or investigate a variety of clinical conditions including heart failure, heart murmurs, atrial septal defects or patent foramen ovale (Sharpey-Schafer 1955, Zema *et al.* 1980, Ferguson *et al.* 1989, Di Tullio *et al.* 1993, Zema 1999, Nishimura & Tajik 2004, Yale 2005a), as well as to test cardiac autonomic function (Levin 1966, Baldwin & Ewing 1977, Palmero *et al.* 1981, Zöllei *et al.* 2003, Junqueira 2008) or to assess cerebral autoregulation (Tiecks *et al.* 1996). As the use of the VM for cardiovascular diagnostic purposes was first described by the German physiologist Edward Weber in 1851 (Derbes & Kerr 1955), it should be actually called in such cases the Weber experiment [as pointed out by Derbes & Kerr (1955)] or at least Valsalva–Weber manoeuvre as suggested by Junqueira (2008); however, to avoid confusion, the traditional term ‘Valsalva manoeuvre’ is used in this article.

### Manoeuvre overview

To perform the VM for cardiovascular diagnostics in a clinical setting, the subject (after being provided with some training) is asked to take a normal or full inspiration and exhale against a closed airway (Junqueira 2008). Such an expiratory effort should create a certain level of intrapleural pressure, which can be estimated by the intra-oral pressure (Elisberg *et al.* 1951) measured through a mouthpiece tubing attached to a manometer (Junqueira 2008) or by the oesophageal pressure measured using a catheter system (Flemale *et al.* 1968). The most common version of the graded VM is an expiratory effort with the intra-oral pressure equal to 40 mmHg which is equivalent to 54 cm of water (this version of the manoeuvre was first introduced by Flack (1920), and is sometimes known also as ‘Flack’s test’ or ‘40 mm Hg test’). The strain should be maintained for a certain period of time (typically 15–20 s; Junqueira 2008), after which the expiratory effort is suddenly released and the respiration should be restored to the normal level (possibly without gasping) (Smith *et al.* 1987, Junqueira 2008).

The diagnosis in the VM is based on heart rate (HR) and arterial BP variations in response to the manoeuvre [with the HR response being more informative (Looga 2005)]. The beat-to-beat HR (or its reciprocal – R-R interval) variations can be measured based on a continuously recorded electrocardiogram, while the arterial BP may be taken directly from a peripheral artery (Junqueira 2008). Both parameters (arterial BP and HR) may also be measured non-invasively using a finger cuff device (e.g. Finapres®), which faithfully represents the systolic and diastolic BPs,

although some small deviations between the measured finger pressures and the brachial intra-arterial pressures have been reported (Imholz *et al.* 1988).

The manoeuvre with the intra-oral pressure monitored as described above must be performed with the open glottis and a constant expiratory muscles contraction to keep the intra-oral and intrathoracic pressures equal (Looga 2005). As the glottis may tend to be closed [allowing the intra-oral pressure to be kept at a high level without the abdominal straining (Looga 2005)], some special measures may be used to keep it open, such as allowing for a small air leakage through the manometer (which, however, can influence the cardiovascular response to the manoeuvre) (Looga 2005). Note that the subjects may also cheat during the test (especially, if it is performed for occupational selection) by closing deliberately the glottis or bringing together the tongue and soft palate, thus being able to keep the intra-oral pressure high without increasing the intrathoracic pressure (Sharpey-Schafer 1955, Looga 2005).

Instead of following an inspiration, the manoeuvre can also be started at the end of an expiration or at some time after or during the preceding inspiration with a possibility of controlling the lung volume, which affects the cardiovascular response (Mateika *et al.* 2002, Looga 2005). Note that the increase of the intrathoracic pressure can also be produced by the pure abdominal straining which involves a similar contraction of the abdominal muscles, but with an inspiratory (as opposed to expiratory) pattern with the diaphragm flattening downwards into the abdominal cavity (rather than upwards into the chest), the pelvic floor muscles staying relaxed (as opposed to contracted) and the closed glottis providing the intrathoracic counter-pressure and blocking the pressurized air from reaching the oronasopharyngeal cavity (Talasiz *et al.* 2011).

The VM with the open glottis or the general abdominal straining with the closed glottis (both resulting in a rise of the intrathoracic pressure and the corresponding cardiovascular response) can also occur spontaneously and unintentionally in everyday life during lifting heavy weights, coughing, vomiting, straining while urinating, during a bowel movement or bearing-down during parturition, as well as during other activities involving straining or blowing against resistance (e.g. blowing up balloons or playing wind instruments) (Smith *et al.* 1996, Jellinek 2006). Apart from the chest expansion and increased abdominal muscle tension, the manoeuvre is accompanied by blushing and jugular vein distension (all the signs being easily observable) (Junqueira 2008).

The reverse of the VM is the Mueller manoeuvre in which, following an expiration, an inspiration attempt

is made with closed mouth and nose, thus causing a reduction of the intrathoracic pressure and the corresponding cardiovascular response with some similarities and differences compared to the VM (Carrasco-Sosa & Guillén-Mandujano 2012).

## Risks

As its adverse effects are extremely rare, the VM is commonly accepted as a safe method of testing cardiac function or the integrity of the autonomic nervous system. However, the manoeuvre is not free of potential side effects, which can include chest pain, syncope, arrhythmia or cerebral stroke (Junqueira 2008), especially in patients with coronary heart disease or cerebrovascular disease (Levine *et al.* 1966). The reduction of left ventricular stroke volume during the manoeuvre combined with inefficient autonomic regulation may even contribute to a transient ventricular arrest (Schartum 1968) or even a sudden death, as it has been reported (Greenfield *et al.* 1967). The manoeuvre results also in an increased intra-ocular pressure which can lead to retinal or macular haemorrhage (Valsalva retinopathy or maculopathy) (Kadmas & Pach 1995, Chapman-Davies & Lazarevic 2002, Gibran *et al.* 2007). Some adverse effects may also include headaches, dizziness, nausea or altered vision (Greenfield *et al.* 1967). A case was reported when the VM performed during airplane descent to relieve ear block caused the Wunderlich syndrome (ruptured renal angiomyolipoma) (Lin *et al.* 2008). There is also a hypothesis that a frequent repetitive execution of the forceful VM may lead to an increased risk of Alzheimer's disease (Wostyn *et al.* 2009). Despite the above, the VM is still considered a very low-risk procedure and is widely used in clinical practice, although it is recommended to perform it with particular caution and emergency equipment available in patients with coronary artery disease (Zema *et al.* 1980) or in subjects known to be sensitive to sudden changes of arterial pressure or HR (Junqueira 2008). In several large studies of autonomic tests including the VM (the largest one covering approx. 20 000 tests), no complications were observed (Low 1993, American Academy of Neurology, 1996). Also in the personal experience of the author (FB), who has over-viewed more than 3000 VMs in three Italian laboratories, no complications were observed (Bellavere 2011).

## Applications

Apart from its use in otolaryngology and cardiology or neurocardiology, the VM has a wide range of diagnostic or instrumental applications in several other disciplines (Yale 2005b). It can be used for inflating

the laryngopharynx in radiology (Editorial, 1970), to diagnose oro-antral communication following dental extractions (Kretzschmar & Kretzschmar 2003), to equalize pressure between the ears and sinuses following ambient pressure changes (e.g. in air travel or diving) (Taylor 1996, Lin *et al.* 2008, Perišić *et al.* 2011) or to protect from middle ear trauma during the hyperbaric oxygen therapy (Lima *et al.* 2012). It can also bring relief of angina pectoris (probably due to reduced oxygen demand of the heart during the manoeuvre) (Levine *et al.* 1966, Federici *et al.* 2000). The VM is also used for assessing the sphincter function and diagnosing urinary incontinence with the so-called Valsalva leak pressure indicating the pressure associated with urine leakage (Lane & Shah 2000, Junqueira 2008) or to assess the female pelvic organ mobility (Mulder *et al.* 2012). The manoeuvre is also used in testing the suturing against dural tear following a spinal surgery (Wolff *et al.* 2012).

As the haemodynamic response to the VM is similar to the effect of positive pressure ventilation (Shekerdemian & Bohn 1999, Vieillard-Baron *et al.* 2004), the pulse pressure variations or systolic pressure variations during the VM can be used as dynamic preload indices for predicting fluid responsiveness in spontaneously breathing critical care patients (Monge García *et al.* 2009, Rehberg *et al.* 2009).

The VM is also used by some athletes to improve their performance, especially in weightlifting or powerlifting. However, given the contradictory results regarding whether the increased intrathoracic and intra-abdominal pressure improves trunk stability and increases the maximal muscle force in the limbs (Findley *et al.* 2003, Hagins *et al.* 2006), as well as due to the potential risks associated with the VM [such as a blackout upon standing during lifting a maximum load (Compton *et al.* 1973)], it is recommended to avoid the VM during high-level exercise (O'Connor *et al.* 1989) and to use forced exhalation instead (Zat-siorsky & Kraemer 2006, Ikeda *et al.* 2009). Although when the force production exceeds approx. 80% of the maximal level, the VM becomes unavoidable (MacDougall *et al.* 1992).

The VM performed voluntarily or as involuntary response to a sudden squeezing of the chest, combined with standing from the squatting position and a prior hyperventilation, is sometimes used by children or high school students to deliberately induce syncope (so-called fainting lark or a mess trick) (Howard *et al.* 1951). While this is done typically as a form of entertainment or to avoid an undesirable task (e.g. an examination), it may be the source of a serious epidemic syncope (Lee *et al.* 1996, Wieling *et al.* 2004).

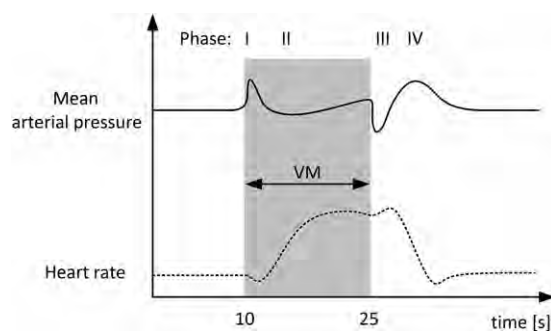
Finally, the VM is also used for selection of staff in specific professions (in diving or air force) (Perišić

*et al.* 2011) and is a very illustrative method of teaching cardiac autonomic function (Junqueira 2008).

### Cardiovascular response

The complex haemodynamic response to the VM reflects both the mechanical impact of the increased intrathoracic and intra-abdominal pressure as well as the action of the autonomic nervous system (through both parasympathetic and sympathetic pathways) responding to the emergent changes in the cardiovascular system (Korner *et al.* 1976). The regulatory mechanisms involve mainly baroreflex with some influence from the slowly adapting pulmonary stretch receptors as well as central and peripheral chemoreceptors (Eckberg 1980, Looga 1997, Mateika *et al.* 2002, Junqueira 2008). The baroreflex responses are initiated mainly by the activity of arterial (carotid) and aortic baroreceptors, with relatively small influence of cardiopulmonary baroreceptors (Smith *et al.* 1996). The impact of non-autonomic humoral mechanisms (e.g. angiotensin II or vasopressin) is negligible given the short timescale of the manoeuvre (Korner *et al.* 1976).

The concomitant variations in HR and arterial BP [the latter being both the effect and source of autonomic reflex responses (Eckberg 1980)] during and after the typical graded VM can be divided into four physiological phases (Hamilton *et al.* 1936). The phases are as follows (see Fig. 1): (I) onset of strain with a rise of arterial pressure and a decrease of HR, (II) continued strain with a drop of arterial pressure and its later partial recovery due to the reflex tachycardia and the progressing vasoconstriction, (III) strain release with a sudden drop of arterial pressure and a further heart acceleration, (IV) system recovery with arterial pressure overshoot and the resulting bradycardia, until the BP and HR normalize. The inspiration of various grade preceding the manoeuvre can be treated as phase 0 (Looga 2005).



**Figure 1** Representation of the typical mean arterial pressure and heart rate variations during and after the Valsalva manoeuvre with normal inspiration before the manoeuvre (no phase 0).

The haemodynamic changes during the VM are relatively rapid, particularly at the onset of the manoeuvre and following the strain release. Given the time constants of the regulatory mechanisms, the system does not reach steady state during the strain (phase II), for which minimum 30 s would be needed (Korner *et al.* 1976).

### Physiology insights

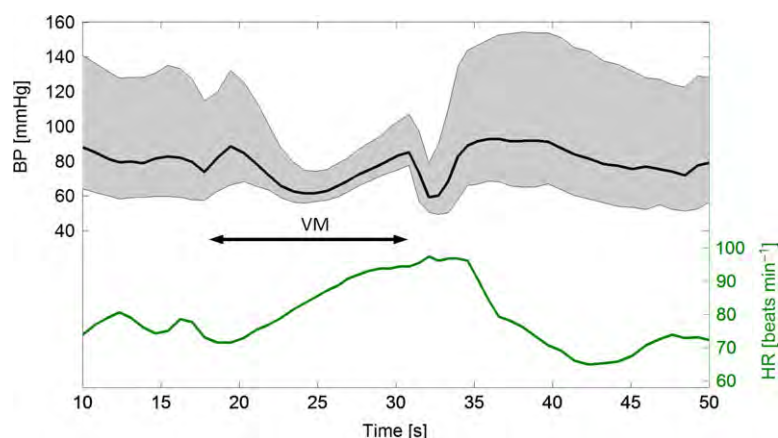
As already mentioned, the cardiovascular response to the VM reflects the action of several regulatory mechanisms. Depending on the phase of the manoeuvre, different mechanisms may act in synergism or in antagonism (Smith *et al.* 1996, Looga 1997, 2005). A detailed description of haemodynamic and neurohormonal alterations during the individual phases of the VM in a healthy individual is provided below. A clinical example of a normal cardiovascular response to the VM is also presented here (Fig. 2) to support the explanations (for more clinical examples and their description, please see the last part of the article).

#### Phase 0 (deep inspiration)

If a deep inspiration precedes the manoeuvre, by reducing the intrapleural pressure, it promotes venous return of blood to the heart and hence increases the intrathoracic blood volume. As a result, the arterial pressure drops causing a reflex tachycardia and peripheral vasoconstriction (deep inspiration vasoconstriction), which consequently lead to arterial pressure increase (Looga 1997, 2001). However, in routine autonomic testing, this phase is usually not applicable, as a normal inspiration is typically suggested before starting the manoeuvre (to minimize the results variation, which could be caused by a variable depth of inspiration between different patients or in the same patient between different tests) (Spallone *et al.* 2011).

#### Phase I (onset of strain)

Straining and forced exhalation against the closed airway increases the intrathoracic and intra-abdominal pressure and hence increases the pressure in all blood vessels within the chest and abdomen including the superior and inferior vena cavae (Sarnoff *et al.* 1948, Gindea *et al.* 1990), as well as in the cardiac chambers (Levin 1966, Korner *et al.* 1976) [the BP increase is approximately equal to the increase in the intrapleural pressure or oesophageal pressure (Stone *et al.* 1965, Fox *et al.* 1966)]. Compression of the aorta causes an immediate transfer of blood to peripheral arteries, thus increasing directly the arterial BP and 'transmitting' the intrathoracic pressure to the rest of



**Figure 2** The arterial blood pressure (mean, diastolic and systolic) and heart rate response to the Valsalva manoeuvre in a 63-year-old male with normal autonomic function.

the circulation (Elisberg 1963, Smith *et al.* 1987). Both diastolic and systolic pressure increase with no significant change in pulse pressure (Stone *et al.* 1965) (see Fig. 2). The magnitude of the arterial pressure rise reflects the vascular properties (elastance/compliance) of both aorta (from which blood is ‘pushed out’) and the whole arterial tree (which accommodates the incoming aortic blood). The pulmonary vessels and cardiac chambers cannot be compressed immediately to the same extent, as the blood outflow from the cardiopulmonary system is ultimately governed by the Frank–Starling law of the heart (Katz 2002) and hence, the blood is ‘squeezed’ out of the pulmonary circulation less abruptly. Within the heart, the declining preload causes a reduction of the cardiac fibre shortening velocity, which is however compensated by the reduced afterload (compressed aorta), with the net result being a slight increase of the fibre shortening velocity (Buda *et al.* 1979). No change in stroke volume can be observed in this phase (Greenfield *et al.* 1967, Smith *et al.* 1987); however, there might be a slight increase in cardiac output resulting from a small gain in HR probably due to withdrawal of parasympathetic tone after the last inspiration or the body agitation at the onset of the manoeuvre (Smith *et al.* 1987). This rise in cardiac output can contribute somewhat to the arterial pressure surge (Smith *et al.* 1987). On the venous part of the circulation, blood from the superior and inferior vena cavae is pushed back to large veins with a corresponding rise in their transmural pressure (Gindea *et al.* 1990). In fact, the increased intrathoracic pressure is transmitted from vena cavae back to venous valves (Sharpey-Schafer 1955). As the strain pressure is transmitted to the venous pressure as well as to the intracranial pressure, the rise in cerebral blood flow is somewhat limited, thus protecting the brain from hyperperfusion injury (cerebral autoregulation alone would be too slow for a complete protection) (Greenfield *et al.* 1984, Tiecks *et al.* 1995, Perry *et al.* 2014b).

The rise in the arterial pressure (sensed by arterial baroreceptors) and, to a lower degree, the decreased transmural pressure in the right atrium and the pulmonary vessels (sensed by low-pressure cardiopulmonary baroreceptors) both trigger a decrease in HR (through increased parasympathetic activity) and a reduction of the peripheral resistance (through inhibition of sympathetic activity) (Eckberg 1980, Looga 2005). In consequence, the arterial pressure starts to decline. This reflex compensatory response is enhanced by the vasodilating depressor reflex from the slowly adapting pulmonary stretch receptors, but on the other hand, it can be slightly lowered due to reduced firing of aortic baroreceptors following the reduction of aortic transmural pressure (Eckberg 1980). However, the activity of carotid baroreceptors seems to have priority over the aortic baroreceptors (Smith *et al.* 1996).

#### Early phase II (continued strain)

The elevated intrathoracic and intra-abdominal pressure impedes venous return to the heart (Sharpey-Schafer 1955, Gindea *et al.* 1990). Compression of the superior vena cava leads to a significant reduction of its lumen (which in some cases may even be totally closed, especially in the early stage of straining), and consequently, the blood flow in the superior vena cava is significantly decreased and may even be stopped (Gindea *et al.* 1990, Attubato *et al.* 1994). Interestingly, the velocity of the remaining blood flow in the superior vena cava increases (due to the dramatic reduction of the lumen) (Gindea *et al.* 1990, Attubato *et al.* 1994). The impeded venous return leads consequently to the transfer of blood from the thorax and abdomen to the limbs (Eckberg 1980) and a gradual rise in the peripheral venous pressure (Rushmer 1947) noticeable by distension of the jugular vein, which is considered a crucial sign of a well-executed manoeuvre (Attubato *et al.* 1994, Junqueira 2008). The blood flow towards the heart may only be restored once the



peripheral venous pressure exceeds the pressure in vena cavae (which is approximately equal to the intrathoracic pressure) (Gindea *et al.* 1990).

Decreasing left atrial pressure causes a reduction in the left ventricle end-diastolic volume, end-systolic volume, stroke volume and cardiac output and hence a gradual decrease in arterial pressure (both systolic and diastolic) from the initially elevated level (Fox *et al.* 1966, Brooker *et al.* 1974, Parisi *et al.* 1976, Smith *et al.* 1996). The decrease in left ventricular stroke volume may even exceed 50% (Greenfield *et al.* 1967, Brooker *et al.* 1974, Parisi *et al.* 1976). As before, the reduction of stroke volume is partly compensated by the reduced afterload. The ejection fraction may go slightly down compared to the control value, although the changes are not significant (Brooker *et al.* 1974). Cardiac output is reduced by approx. 50% (Brooker *et al.* 1974). The blood flow in the thoracic aorta may decrease down to 35% of the control flow before the manoeuvre (Fox *et al.* 1966). Emptying of pulmonary vessels and cardiac chambers [associated with the reduced atrial and ventricular dimensions (Eckberg 1980)] may even lead in some cases to a momentary circulation arrest lasting a few seconds (Fox *et al.* 1966, Looga 2005).

The diastolic pressure does not typically drop below the baseline level (Elisberg *et al.* 1953, Brooker *et al.* 1974, Smith *et al.* 1996, Zhang *et al.* 2004); however, the systolic pressure decreases significantly more [due to the reduced stroke volume ejected to the emptied aorta (Brooker *et al.* 1974)], and hence, the pulse pressure is reduced (Sharpey-Schafer 1955) (see Fig. 2). The mean arterial pressure drops hence slightly below the baseline level (Stone *et al.* 1965, Zhang *et al.* 2004). Similarly, the pulse pressure in the pulmonary arteries also decreases (Fox *et al.* 1966).

At the same time, the peripheral venous pressure continues to rise (due to accumulation of blood). The rate of peripheral venous pressure increase depends mainly on the vasomotor tone of skin and muscle vessels in the limbs (being higher in the more dilated states, e.g. in hot limbs) (Sharpey-Schafer 1955).

In case of a very high intrathoracic pressure (like in weight-lifting or playing wind instruments), the markedly reduced arterial pressure combined with an elevated venous pressure may lead to a significant reduction of cerebral perfusion pressure and hence even an occasional fainting, especially in the standing position (Pott *et al.* 2000).

#### Late phase II (pressure recovery)

The reduced aortic and arterial pressure (sensed by aortic and arterial baroreceptors), as well as decreased pulse pressure (Sharpey-Schafer 1955, Stone *et al.*

1965, Levin 1966), cause a rise of systemic resistance [due to increased sympathetic activity (Delius *et al.* 1972, Smith *et al.* 1996, Sandroni *et al.* 2000)], a sympathetic stimulation of the heart (Elisberg 1963, Palmero *et al.* 1981) and the corresponding tachycardia [mainly due to withdrawal of parasympathetic activity (Eckberg 1980)]. Sympathetic activation occurs after some time lag (Delius *et al.* 1972, Smith *et al.* 1996) and is supported also in part by peripheral chemoreceptors due to hypercapnia and hypoxia (Elisberg *et al.* 1953). The impact of chemoreceptors is, however, relatively small and restricted to the late stage of straining, given that they start to act only after a few seconds of hypoxia, which itself will not manifest until a few seconds following the start of the manoeuvre.

The increasing HR compensates for the reduced stroke volume and thus prevents further reduction of cardiac output as well as, together with the elevated peripheral systemic resistance, prevents the further arterial pressure decline and leads to its subsequent recovery above the baseline level (Stone *et al.* 1965, Hébert *et al.* 1998, Zhang *et al.* 2004) (see Fig. 2). The sympathetic activity may be reduced by antagonistic sympathoinhibitory signals from cardiopulmonary baroreceptors and slowly adapting pulmonary stretch receptors (Looga 2005). No significant change in pulse pressure is associated with the arterial pressure recovery in this phase (Stone *et al.* 1965, Hébert *et al.* 1998). In the pulmonary arteries, no pronounced pressure recovery has been observed, which is probably associated with the lack of pulmonary arteriolar constriction (Lee *et al.* 1954).

#### Phase III (release)

As soon as the strain pressure is released and the intrathoracic pressure goes back to normal level, the absolute pressure in the thoracic vasculature drops approximately by the value of the withdrawn strain pressure, which is hence no longer transmitted to the rest of the circulation (Stone *et al.* 1965). Moreover, the significant fraction of left ventricular output is used to fill up the previously compressed aorta (Greenfield *et al.* 1967), which temporarily reduces the blood flow to systemic arteries and also reduces slightly the left ventricular stroke volume (by increasing the afterload) (Eckberg 1980). At the same time, a sudden drop of central venous pressure causes the expansion of the superior and inferior vena cavae (Gindea *et al.* 1990) and an increased flow of blood accumulated in the venous reservoir towards the heart (Gindea *et al.* 1990) resulting in a decrease of the peripheral venous pressure. All these effects lead to a precipitous drop in the systemic arterial pressure (see

Fig. 2). Both diastolic and systolic pressures fall below control level (Stone *et al.* 1965), with a small drop in pulse pressure (Stone *et al.* 1965, Hébert *et al.* 1998). Similarly to the aorta and superior and inferior vena cavae, the volume and transmural pressure of the pulmonary vessels increase as well (Eckberg 1980), and hence, the output of the left ventricle is lower than the output of right ventricle, which is used in part for filling up the pulmonary bed (Sarnoff *et al.* 1948). The increased heart filling compensates the increased afterload, so that the stroke volume is reduced only lightly or does not change at all (Greenfield *et al.* 1967).

Upon releasing the strain pressure, the marked arterial pressure drop is very rapid, and hence, syncope or pre-syncope symptoms (e.g. dizziness) may potentially occur (even in healthy subjects), especially during an intense VM in the standing position (the cerebral autoregulation is too slow to immediately counteract this hypotension; however, eventually it does limit the brain hypoperfusion) (Greenfield *et al.* 1984, Perry *et al.* 2014b).

The decrease of arterial pressure entails a further increase in sympathetic activity (from the already elevated level) and an additional, albeit minor, reflex increase in the systemic resistance and HR (Elisberg 1963, Gindea *et al.* 1990). The cardiovascular response in this phase of the manoeuvre may be affected by the rate of the post-strain breathing, especially the first deep inspiration after the manoeuvre, when the lungs expand rapidly (Looga 2005).

#### Phase IV (recovery)

The restoration of venous return causes a continuous rise in diastolic heart filling, thus improving the cardiac function. The ejection fraction may also go slightly above the control value, although the changes are not great (Brooker *et al.* 1974). Both increased filling and improved ejection fraction lead to an increased stroke volume (in both right and left ventricles) reaching the maximum after 6–15 heart beats following the pressure release (Greenfield *et al.* 1967) at the level approx. 25% greater than the control value (Greenfield *et al.* 1967). The increase in cardiac output over 40% above the control resting value was reported (Brooker *et al.* 1974). In the consequence, the arterial pressure starts to recover.

Meanwhile, even though the peripheral sympathetic system activity is low at this stage (Delius *et al.* 1972, Smith *et al.* 1996) (associated only with the activity of cardiopulmonary baroreceptors subject to an elevated transmural pressure), the systemic resistance is still elevated as a result of the sympathetic activity in previous phases of the manoeuvre (Green-

field *et al.* 1967, Smith *et al.* 1996). This is due both to the fact that the previously released noradrenaline is still circulating in the system, thus preventing the vessels to dilate, and to the inertia of the constricted vessels (Delius *et al.* 1972). The high blood volume ejected from the left ventricle to the constricted arterial tree leads therefore to a significant increase in the arterial pressure (so-called pressure overshoot) (Sarnoff *et al.* 1948, Elisberg 1963, Levin 1966, Eckberg 1980) (see Fig. 2). The arterial BP rises in this phase typically 20–40 mmHg above the baseline pressure, although in some individuals, it can increase even to 80 mmHg above control values. As systolic pressure rises more than diastolic, there is an increase in pulse pressure (McIntosh *et al.* 1954, Stone *et al.* 1965, Hébert *et al.* 1998). Interestingly, vasoconstriction alone would not cause a pressure overshoot if there was no increase in the blood flow, as observed in cardiac failure (Stone *et al.* 1965, Levin 1966). This is why a similar, albeit smaller pressure overshoot can be observed in the pulmonary arteries (where vasoconstriction does not occur) (Lee *et al.* 1954, Stone *et al.* 1965). The magnitude of the arterial pressure overshoot is directly related to the left ventricular ejection fraction and inversely related to the left ventricular end-diastolic pressure (Zema *et al.* 1980).

The arterial pressure overshoot combined with the drop in venous pressure and intracranial pressure, as well as the dilated state of cerebral arteries [as a result of cerebral autoregulation in previous phases and reactive hyperaemia response (Perry *et al.* 2014a)], means that this phase is associated with the highest risk of potential aneurysm rupture (Tiecks *et al.* 1995).

The activity of arterial and aortic baroreceptors [responding both to the increased level of pressure as well as to the increased pulse pressure (Looga 2005)] initiates then the compensatory reflex response resulting in relatively quick slowing down of the heart (related almost entirely to the increased parasympathetic activity) (Elisberg *et al.* 1953, Elisberg 1963, Junqueira 2008). The reduction of peripheral resistance (being still high despite the lack of sympathetic activity) is delayed, for the reasons already indicated. The depressor response in this phase of the manoeuvre may be reduced by the antagonistic pressor activity from cardiopulmonary baroreceptors (Looga 2005) [subject to an elevated transmural pressure from the increased venous return (Fox *et al.* 1966)]. The cardiovascular response in this phase may also be affected by arterial blood gases (oxygen and carbon dioxide) (Mateika *et al.* 2002). The relatively sudden reduction of HR (bradycardia) is used in clinical practice to arrest episodes of paroxysmal supraventricular tachycardia (Lim *et al.* 1998, Smith *et al.* 2009),

which is not however free of potential adverse effects (Nagappan *et al.* 2002).

Eventually, the HR and systemic resistance reach their basal values with a complete system recovery back to the normal steady state equilibrium. It has been measured that the average time for both systolic and diastolic arterial pressure to return to the baseline value after a 15-s VM with the strain pressure of 30 mmHg was approx. 25 s (Smith *et al.* 1996). For the standard strain pressure of 40 mmHg, the full recovery would take approx. 5 s more.

### Factors influencing the cardiovascular response

The duration of the manoeuvre, the strain level and the rate of pressure changes all influence the cardiovascular response to the manoeuvre (Looga 2005, Junqueira 2008). For lower strain pressures, the intrastrain hypotension and tachycardia as well as the post-strain hypertension and bradycardia are less marked, while for higher strain levels, the opposite effect can be observed (Smith *et al.* 1996, Looga 2005). Some authors discourage performing the shorter or longer manoeuvre or reaching lower strain pressures during the manoeuvre (Junqueira 2008), while others consider performing a number of manoeuvres under different conditions desirable for a more comprehensive diagnostics (Looga 2005).

The magnitude of arterial pressure drop in early phase II and its further recovery in late phase II depends also on the fractional reduction of the thoracic blood volume (reflecting the impeded venous return) – the lower the thoracic blood volume, the greater the arterial pressure decrease and the smaller pressure recovery (Stewart *et al.* 2004). The restoration of impeded venous return reflects the properties of the peripheral veins (resistance and compliance) – the higher the peripheral venous pressure increase rate, the shorter the time to the restoration of heart filling and hence the faster the arterial pressure recovery in late phase II (with the concomitant contribution from the sympathetic nervous system) (Stewart *et al.* 2004).

The manoeuvre is usually performed in the supine position, although other body positions (sitting, squatting or standing) are also possible with a significant impact on the manoeuvre effects (Pott *et al.* 2000, Singer *et al.* 2001, Junqueira 2008, Vogel *et al.* 2008, Perry *et al.* 2014b). When the manoeuvre is performed in the supine position, the cardiovascular response in late phase II and phase IV is less marked (Ten Harkel *et al.* 1990) (most probably due to the fact that the larger intrathoracic blood volume in the supine position buffers to some extent the reduced venous return) (Sandroni *et al.* 1985). In the sitting or standing posi-

tion, the changes are more conspicuous (Greenfield *et al.* 1967, Luster *et al.* 1996, Singer *et al.* 2001).

Fluid status has a similar impact on the cardiovascular response to the VM, with hypovolaemia increasing the magnitude of response, while hypervolaemia attenuating the response or even changing the response to a square wave type pressure response (discussed later) (Fritsch-Yelle *et al.* 1999).

The duration and position of rest before the manoeuvre also affect the results (Wieling & Karemaker 2013), although the relatively subtle effects of the supine rest before the manoeuvre are typically overpassed by strong mechanical effects at the onset of the manoeuvre (Ten Harkel *et al.* 1990). The rate of the inspiration before the manoeuvre affects the cardiovascular response (especially in phase I) (Looga 2005). As in other cardiovascular reflex tests, the time of the day, the room temperature, the prior food and fluid intake or the use of caffeine or cigarettes, as well as some medications, may all affect the cardiovascular response to the VM (Wieling & Karemaker 2013). The manner of starting the manoeuvre itself can also have an impact, with a voluntary start being less distressing than a start following a visual or sonic signal (Looga 2005).

The manoeuvre started at the end of an expiration will feature a higher magnitude of cardiovascular changes compared to the inspiratory variant (Mateika *et al.* 2002, Looga 2005), as well as a higher arterial pressure throughout the manoeuvre (Rushmer 1947), which can be explained by the lack of antagonistic reflex responses originated from the pulmonary stretch receptors (Looga 2001), the differences in blood gases (Mateika *et al.* 2002) or the pressure gradient between the abdomen and thorax promoting venous return (Rushmer 1947). In some cases, the expiratory version of the manoeuvre may even cause a square wave pressure response (Mateika *et al.* 2002).

No differences in the arterial pressure and HR response to the VM between the physically trained and untrained subjects have been observed (Fuenmayor *et al.* 1992). The cardiovascular response to the VM depends, however, on the subject's age (with the magnitude of responses decreasing with age due to decreased venous compliance, reduced baroreflex sensitivity or increased thoracic blood volume) (Levin 1966, Baldwin & Ewing 1977, Kalbfleisch *et al.* 1977, Wieling & Karemaker 2013).

### Role of the autonomic system

The arterial BP changes during the VM are purely mechanical in phases I and III (Sandroni *et al.* 1985), as well as early phase II (Looga 2005), while in phases II and IV, they reflect the cardiac function and



autonomic reflexes. Note that, given the resetting of baroreceptors after a few seconds of intense activity, the baroreflex control mechanisms reflect the ongoing changes in the BP rather than the difference in pressure with respect to the original baseline level (van Lieshout *et al.* 1989, Smith *et al.* 1996). The cardiovascular response in individual phases of the manoeuvre reflects the action of different autonomic mechanisms, the role of which is best shown following a partial or full autonomic blockade.

Interestingly, a given phase may be controlled by different mechanisms depending on the body position (Sandroni *et al.* 1985). In patients in the supine position,  $\alpha$ -adrenergic blockade (with  $\alpha$ -adrenergic antagonists) causes an exaggerated hypotension in the early phase II and a significantly reduced or absent arterial pressure recovery in late phase II, while slightly increasing the cardiovascular response in phase IV (Sandroni *et al.* 1985) [probably due to increased sympathetic activity and tachycardia in response to a larger hypotension (Sharpey-Schafer 1955)]. On the other hand,  $\beta$ -adrenergic blockade (with non-selective beta-blockers) causes a marked reduction in phase IV with little or no impact on late phase II (Sandroni *et al.* 1985). This shows that, with the patient in the supine position, the arterial pressure recovery in late phase II is mediated mainly by the  $\alpha$ -adrenergic system, while the pressure overshoot in phase IV is mainly due to  $\beta$ -adrenergic system (Sandroni *et al.* 1985, 2000). In sitting or standing patients, on the other hand, a marked reduction in phase IV can be observed following the use of  $\alpha$ -antagonists, which can be explained by a greater reduction in venous return (compared to the VM in the supine position) due to an increased vascular capacity (Sandroni *et al.* 2000).

The use of ganglionic blockers (e.g. tetraethylammonium) abolishes the arterial pressure overshoot in phase IV due to the general blockade of the autonomic system (Sarnoff *et al.* 1948, Bunnell *et al.* 1951, Elisberg *et al.* 1953). This may be however not the effect of lack of tachycardia and vasoconstriction, rather the effect of pooling of blood in limbs or splanchnic bed, thus reducing venous return (Stone *et al.* 1965). With the total autonomic blockade, the phases I and III remain unchanged proving that the arterial pressure changes in these phases are of purely mechanical origin (Korner *et al.* 1976).

The use of muscarinic receptors antagonists (e.g. atropine) increases both the magnitude and duration of the arterial pressure overshoot in phase IV by counteracting the parasympathetic system and causing an increase in HR instead of the normal bradycardia (Elisberg *et al.* 1953, Elisberg 1963). Vagal denervation would cause a similar effect (Sarnoff *et al.* 1948). With the total blockade of cardiac autonomic effectors

(e.g. with atropine and propranolol), the HR changes are markedly attenuated, while the arterial pressure profile remains unaffected or mildly modified (Korner *et al.* 1976).

### Autonomic function assessment

The evaluation of the autonomic function and vagal baroreflex sensitivity is performed based on specific indices extracted from the R-R interval variations such as the relative tachycardia in phases II and III (measured in terms of a change from the control R-R interval before the manoeuvre), relative bradycardia in phase IV (measured analogously), the Valsalva ratio (the ratio between the maximal tachycardia and maximal bradycardia equivalent to the ratio of the longest and shortest R-R interval) (Levin 1966) and the time or velocity of the change from the maximum tachycardia in phase III to the maximum bradycardia in phase IV (i.e. the rate of bradycardic response) (Palmero *et al.* 1981), with the latter being the most sensitive to the mild autonomic dysfunction (Junqueira 2008).

New indices have been recently proposed to assess adrenergic function, such as blood pressure recovery time (PRT, measured from the valley of phase III until BP returns to baseline level) (Vogel *et al.* 2005), adrenergic BRS (defined as systolic pressure drop in phase III divided by PRT) (Schrezenmaier *et al.* 2007) or alternative adrenergic BRS (in which a weighted sum of BP decrements from early phase II and phase III is divided by PRT) (Huang *et al.* 2007, Schrezenmaier *et al.* 2007). More recently, a modified version of PRT (measured from the early phase II) was suggested for calculating adrenergic BRS (Palamarchuk *et al.* 2014).

For an accurate diagnosis, the manoeuvre should be preferably performed several times [e.g. three or four (Junqueira 2008)], with sufficient time between each experiment (5–10 min) (Junqueira 2008), taking the mean values of the calculated indices or duration of R-R interval changes (Junqueira 2008). The normal values of the most used indices are as follows: the Valsalva ratio >1.5 (Levin 1966) [more detailed age-related normal values are provided in Spallone *et al.* (2011)], the time from the maximum tachycardia to the minimum bradycardia shorter than 24.7 s, the velocity of bradycardia response >2.4% per second (Junqueira 2008).

The Valsalva ratio is inversely related to the left ventricular end-diastolic pressure, and it decreases with increasing severity of dyspnoea (Levin 1966). On the other hand, it increases with increasing strain pressure (Levin 1966).

The baseline HR and arterial BP (to which the measured values are compared) are taken as mean values

recorded before the manoeuvre, once they stabilize [to overcome subject's anxiety or excitation, a controlled respiration may be employed (Looga 2005)]. Note that the cardiovascular response to the VM depends on the baseline HR, and hence, the same subject may have different response at different times (Looga 2005).

### Abnormal responses

Several types of characteristic cardiovascular responses to the VM have been reported in patients with some pathologies or in normal patients subject to certain specific conditions during the VM.

One of the typical abnormalities is the intrastrain bradycardia instead of tachycardia in subjects with a vagotonic state of autonomic reactivity or in conditions of fully expanded lungs (Looga 2001, Junqueira 2008). Such intrastrain bradycardia occurs when the vagal reflex from the slowly adapting pulmonary stretch receptors surpasses the sympathetic reflex from arterial baroreceptors and is therefore likely to occur especially at low strain pressures when pulmonary stretch receptors are subject to higher deviations from baseline levels than arterial baroreceptors (Looga 2001). The intrastrain bradycardia following a deep inspiration before the manoeuvre is typically decreased (or even replaced by tachycardia) in case of small air leakage (to keep the glottis open) (Looga 2001).

Another common abnormality is the lack of arterial pressure decrease in the early phase II characterized by a square wave (or flat-top) pressure response with no change of pulse pressure, a diminished or absent tachycardia in phase II and no bradycardia in phase IV. This response can occur in patients with impaired ventricular function or in some patients with mitral stenosis, constrictive pericarditis or atrial septal defects (Levin 1966, Greenfield *et al.* 1967, Parisi *et al.* 1976, Zema *et al.* 1980) and can be explained either by the patient operating on the horizontal part of the ventricular function curve (Levin 1966) or by the increased intrathoracic blood volume (Hancock *et al.* 1963), with both cases implying that the changes in venous return do not affect left ventricular stroke volume (Levin 1966). In severe heart failure, the VM may even cause an increase in pulse pressure, if the heart operates on the failing limb of the Frank-Starling curve, in which case a decrease in venous return and filling pressure may increase the stroke volume (Sharpey-Schafer 1955, Ruskin *et al.* 1968). A square wave pressure response to the VM can also be observed in healthy subjects in the supine or sitting position with the response changing to a normal 'sinusoidal' pressure response upon sitting or standing respectively (Ten Harkel *et al.* 1990, Singer *et al.* 2001). This indicates that for diagnosing

heart failure, the manoeuvre should be preferably performed in the sitting or standing position ideally accompanied by echocardiography (Parisi *et al.* 1976). On the other hand, a greater orthostatic stress with associated sympathetic activity in the sitting or standing position may distort the assessment of baroreflex sensitivity (Luster *et al.* 1996, Singer *et al.* 2001). A 20° head-up tilt position can often be sufficient to reduce the incidence of square wave responses to the VM and provide a normal response in phase II and IV, while not inducing a significant orthostatic stress (Vogel *et al.* 2008).

The lack of phase IV can also be observed in patients with valvular disease, constrictive pericarditis or pulmonary vascular disease (Elisberg *et al.* 1953). In general, lack of pressure overshoot occurs when the heart cannot increase stroke volume for increased venous return (Stone *et al.* 1965). Similarly, the lack of pressure recovery in late phase II occurs when the cardiac output is not increased with tachycardia (Stone *et al.* 1965). Such attenuation of late phase II response can be seen, for instance, in patients with the history of cerebral syncope (Chuang *et al.* 2005). In patients with non-severe mitral stenosis, there is also a lack of phase IV pressure overshoot; however, instead of the square wave response, a significant reduction in stroke volume and pulse pressure with reflex tachycardia in phase II was reported (Tsai & Chen 1993).

Large hypotension in the early phase II and lack of pressure recovery and pressure overshoot in late phase II and phase IV, respectively, can be observed in patients with orthostatic hypotension ( $\alpha$ -adrenergic failure) (Sandroni *et al.* 1985). Dramatic drops in BP in phase II in subjects with adrenergic dysfunctions may even lead to syncope (Hiner 2005). A reduced pressure recovery in late phase II and reduced pressure overshoot in phase IV can be seen in patients with sympathetic sudomotor failure (mild  $\alpha$ -adrenergic failure) (Sandroni *et al.* 1985). Despite abnormal pressure response, such patients may feature typical HR changes during the VM in case of intact baroreceptor afferent pathways and intact vagal control of heart (except the lack of relative bradycardia in late phase IV given the absence of the pressure overshoot) (van Lieshout *et al.* 1989). A decrease in arterial BP and pulse pressure in early phase II, combined with the lack or minimal pressure recovery in late phase II, but with a relatively high BP overshoot in phase IV, can be seen in patients with postural tachycardia syndrome (Sandroni *et al.* 2000). This can be explained by a partial autonomic neuropathy in which the noradrenaline spillover in venous circulation (particularly in lower extremities) is impaired leading to inhibited venoconstriction and vasoconstriction in lower extremities (Mar & Raj 2014).

The lack of BP overshoot and the corresponding bradycardia in phase IV occurs in patients with defective autonomic system (Hiner 2005), for instance in diabetic-related neuropathy due to impaired baroreceptor afferents (Nathanielsz & Ross 1967).

On the other hand, the arterial BP overshoot in phase IV may be unaccompanied by the reflex bradycardia in case of an intact sympathetic system, but impaired vagal efferent pathways (possible also in diabetic patients) (Baldwa & Ewing 1977, Bennett *et al.* 1978). This shows that for an accurate diagnosis of cardiovagal and adrenergic function, both HR and arterial BP must be recorded during the VM (Bennett *et al.* 1978, Eckberg 1980, van Lieshout *et al.* 1989, Bellavere 1995).

Given the variety of possible cardiovascular responses to the VM, there may be also many intermediate responses, which can be sometimes difficult to interpret (Levin 1966).

### Clinical examples

The clinical examples of normal and abnormal responses to the VM presented below come from cardiovascular reflex tests performed and evaluated in Padua University Hospital in Italy during routinely scheduled ambulatory visits of patients with either prior diagnosis of autonomic neuropathy or at risk of developing autonomic neuropathy in association with other diseases, such as diabetes. The patients (after a written informed consent) were asked to perform a 15-s VM in the sitting position blowing in a specially devised manometer and exerting a constant intra-oral pressure of 40 mmHg (with the glottis kept open). Beat-to-beat arterial BP profiles were measured non-invasively using the Finometer<sup>®</sup> Pro Model 1 (Finapres Medical Systems BV, Amsterdam, the Netherlands). Three-lead ECG signals for real-time assessment of R-R intervals were obtained with a

wireless ECG Monitor Life Scope 8 (Nihon Kohden Italia S.r.l., Bergamo, Italy). Instantaneous BP and ECG analogue signals were sampled at 250 Hz with a 12 bits A/D converter (Measurement Computing Corporation, Norton, MA, USA) following suitable signal preconditioning (low-pass filtering). The software for real-time signal acquisition, visualization and evaluation (iCare) was developed in-house using Visual Studio.NET (Microsoft, Redmond, WA, USA). The software supports the execution of different cardiovascular tests both for a correct timing of the various test-phases and for the calculation of specific indices according to recommended test protocols (Spallone *et al.* 2011). Only selected data from chosen patients were shown here for illustrative purposes.

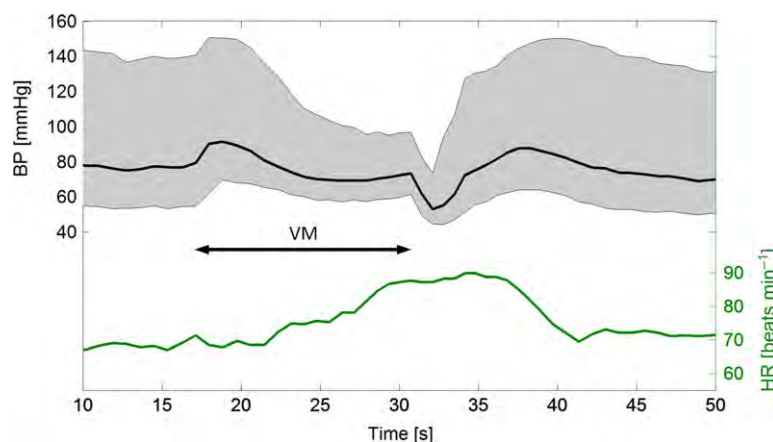
### Discussion

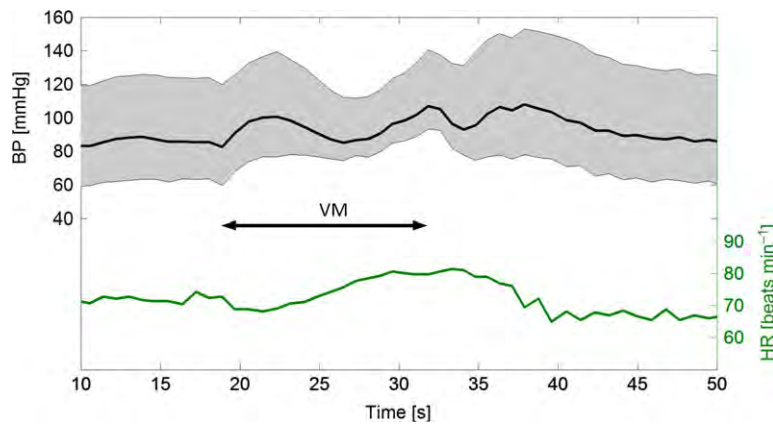
Figure 2 presents a typical cardiovascular response to the VM. The patient (63-year-old male), despite the diabetes and hypertension, presented a normal autonomic response with all four phases of the VM clearly visible. A normal response was also observed in the patient from Figure 3 – a 71-year-old male with previous myocardial infarction, although in this case, the HR response was less pronounced, as expected from the patient's age.

The patient in Figure 4 (a 68-year-old female) had a lower response of HR due to the use of beta-blockers for hypertension. In this case, a higher peripheral vasoconstriction occurred probably to compensate for lower tachycardia or as the effect of the impact of beta-blockers on vascular walls leading to a higher pressure recovery in late phase II and a slightly higher pressure overshoot in phase IV.

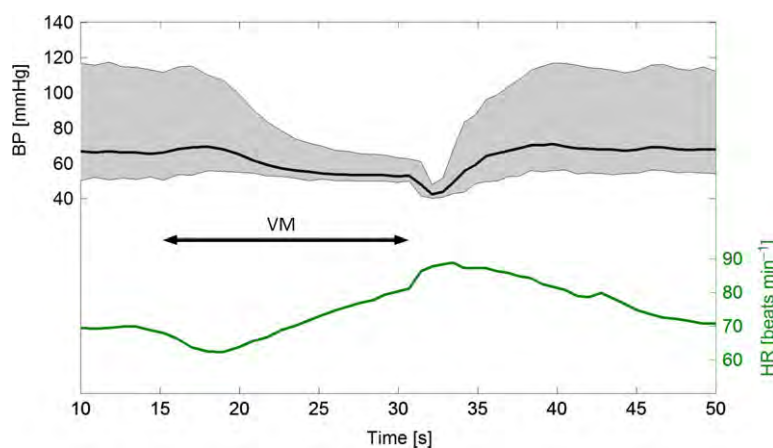
Figure 5 presents a 79-year-old male with postural instability, whose cardiovascular response showed no pressure recovery in late phase II and a relatively small pressure overshoot with no rapid bradycardic

**Figure 3** The arterial blood pressure (mean, diastolic and systolic) and heart rate response to the Valsalva manoeuvre (VM) in a 71-year-old male with a normal autonomic function, although with less pronounced response to the VM compared to the patient from Figure 2.

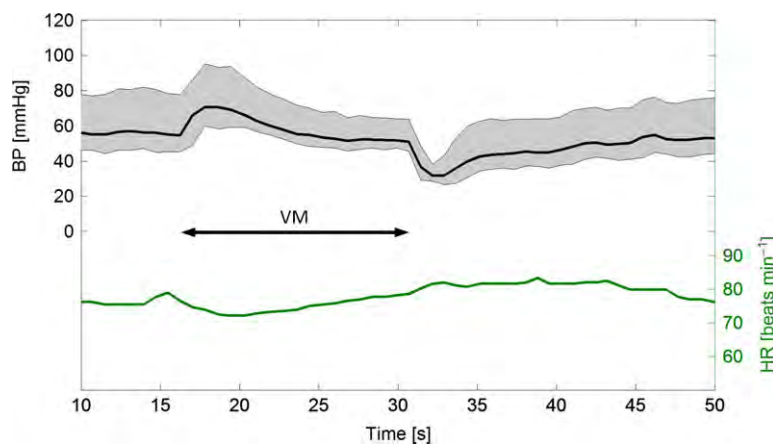




**Figure 4** The arterial blood pressure (mean, diastolic and systolic) and heart rate response to the Valsalva manoeuvre in a 68-year-old female on beta-blockers.



**Figure 5** The arterial blood pressure (mean, diastolic and systolic) and heart rate response to the Valsalva manoeuvre in a 79-year-old male with postural instability.



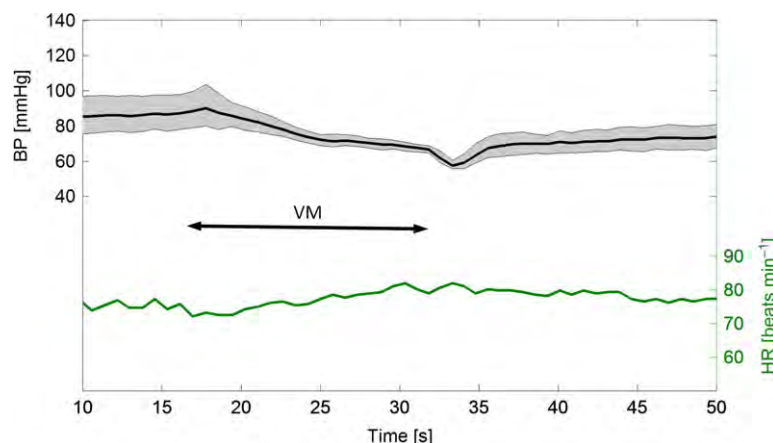
**Figure 6** The arterial blood pressure (mean, diastolic and systolic) and heart rate response to the Valsalva manoeuvre in a 56-year-old male with autonomic neuropathy.

response in phase IV, as can be expected in the early phase of postural orthostatic tachycardia syndrome or in patients with a recurrent vasodepressive syncope.

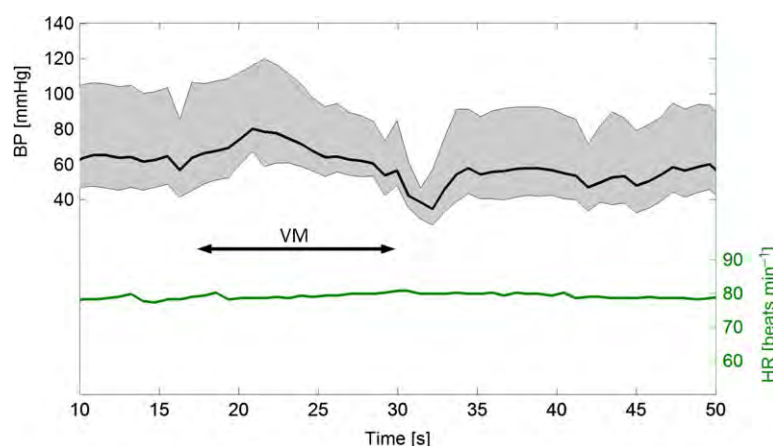
Figure 6 presents a response characteristic for autonomic neuropathy. The patient (a 56-year-old male, who was diagnosed with neurogenic bladder dysfunction and suspected multiple system atrophy) showed

very limited variation in HR and no reflex response in arterial BP. An even lower response was observed in a 83-year-old female with the Parkinson's disease (Fig. 7) or in a 62-year-old female (Fig. 8) with diabetes mellitus and renal complications, who showed almost no changes in HR. All these cases suggest the presence of autonomic neuropathy, as expected in diabetic or renal patients.

**Figure 7** The arterial blood pressure (mean, diastolic and systolic) and heart rate response to the Valsalva manoeuvre in a 83-year-old female with the Parkinson's disease.



**Figure 8** The arterial blood pressure (mean, diastolic and systolic) and heart rate response to the Valsalva manoeuvre in a 62-year-old female with diabetes mellitus and renal complications.



In all patients, there was an evident decrease of pulse pressure during phase II and its further recovery in phase IV.

## Conclusions

As simple as it may sound, the VM produces a complex cardiovascular response with a concomitant action of several regulatory mechanisms. As is evident from the presented clinical data and reviewed literature, the manoeuvre can produce a variety of significantly different responses depending on the functionality of the autonomic nervous system, different conditions or pathologies or the use of medications interacting with the cardiovascular system. As discussed earlier, the response to the VM depends also on patient's body position and the fluid status, as well as on a number of factors associated with the execution of the manoeuvre. Therefore, a deep understanding of the physiological phenomena occurring during and after the VM, the awareness of the interactions between different regulatory mechanisms and a grasp of possible responses seem to be crucial for conducting a proper diagnostic test and evaluating its results.

## Conflict of interest

The authors declare no conflicts of interest.

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