Clinical Neurophysiology 117 (2006) 716–730

www.elsevier.com/locate/clinph

Invited review

Assessment of cardiovascular autonomic function

Roy Freeman *

[a] *Autonomic and Peripheral Nerve Laboratory, Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, 1 Deaconess Road, Boston, MA 02215, USA*
[b] *Department of Medicine, Hospital School of Medicine, Boston, MA, USA*

Accepted 23 September 2005
Available online 7 February 2006

Abstract

Autonomic assessment has played an important role in elucidating the role of the autonomic nervous system in diverse clinical and research settings. The techniques most widely used in the clinical setting entail the measurement of an end-organ response to a physiological provocation. The non-invasive measures of cardiovascular parasympathetic function involve the analysis of heart rate variability while the measures of cardiovascular sympathetic function assess the blood pressure response to physiological stimuli. Prolonged tilt-table testing, with or without pharmacological provocation, has become an important tool in the investigation of a predisposition to neurally mediated (vasovagal) syncope. Frequency domain analyses of heart rate and blood pressure variability, microneurography, occlusion plethysmography, laser Doppler imaging and flowmetry, and cardiac sympathetic imaging are currently research tools but may find a place in the clinical assessment of autonomic function in the future.

Keywords: Parasympathetic nervous system; Sympathetic nervous system; Autonomic nervous system; Autonomic function testing; Autonomic failure; Neurally mediated syncope

1. Introduction

The evaluation of cardiovascular autonomic function is the cornerstone of the clinical investigation of autonomic function. In addition, the measurement of cardiovascular function has become an essential tool in research studies. Autonomic assessment has played and important role in elucidating the role of the autonomic nervous system in diverse conditions such as cardiac arrhythmias, sudden unexplained death, sleep disorders, hypertension and obesity. This review will cover those techniques commonly used in clinical autonomic laboratories as well as those used in the research setting.

Because the anatomic location of the cardiovascular autonomic nervous system renders it inaccessible to simple direct physiological testing, a group of clinical tests measuring cardiovascular autonomic function and dysfunction has been developed to circumvent this problem by measuring the end-organ responses to various physiological and pharmacological perturbations. There are several research tests that allow more direct assessment of autonomic function; sympathetic microneurography—a research technique whereby muscle sympathetic nerve activity can be measured directly from sympathetic nerve fibers in a peripheral nerve, the analysis of catecholamine and catecholamine metabolite levels and cardiovascular autonomic imaging techniques.

2. Clinical tests of cardiovascular autonomic function

2.1. Tests of cardiovagal function

2.1.1. Heart rate variability with deep respiration

Respiratory mediated heart rate variability is the most widely used index of cardiac parasympathetic function. The beat to beat variability of heart rate is predominantly mediated by the vagus nerve. The amplitude of the beat to beat variation with respiration is the most commonly used

* Corresponding author. Tel./fax: +1 617 632 8454.
E-mail address: rfreeman@bidmc.harvard.edu.

1388-2457/$30.00
doi:10.1016/j.clinph.2005.09.027

measure although several additional measures are used, including the standard deviation of the *R–R* interval, the mean square successive difference, the expiratory—inspiratory ratio (*E*:*I* ratio), and the mean circular resultant. The laboratory or bedside tests of heart rate variability with deep breathing are usually performed in the supine position where vagal tone is greatest, however, some authors have advocated the seated position. Typically, the test is performed over 6 respiratory cycles, although some have proposed 10 respiratory cycles, the mean of the 5 largest responses from 8 respiratory cycles or 3 cycles (Freeman, 1997).

There are a number of factors that influence respiratory mediated heart rate variability. Respiratory sinus arrhythmia is dependent on both the frequency and the depth of respiration. That is, the magnitude of change in heart rate at a given respiratory rate is dependent on the tidal volume and, for a specific tidal volume, the magnitude of heart rate variability is dependent on the breathing frequency. Several time and frequency domain studies have suggested that the amplitude of the heart rate increase is maximal at respiratory rates between 5 and 10 breaths per minute (Freeman et al., 1995). Smaller changes in heart rate occur at lower and higher respiratory rates for a given tidal volume (Brown et al., 1993; Eckberg, 1983). The maximal heart rate response in subjects with an autonomic neuropathy occurs at lower respiratory rates (Freeman et al., 1995; Mackay, 1983). Other potential confounders that may reduce respiratory mediated heart rate variability include hypocapnia (that may occur with hyperventilation) (Cooke et al., 1998) and increased sympathetic outflow (Taylor et al., 2001).

There is a well-established relationship between age and heart rate variability. This relationship has been expressed in most studies as a linear decline in the heart rate response to deep breathing with increasing age (Low et al., 1997). These studies suggest a decline in heart rate variability of 3–5 beats per minute per decade in control subjects (regression slope coefficients ranging from approximately 0.35 to 0.46).

The use of a single normative value for all ages will thus reduce the diagnostic discrimination of this test and may result in false negative test results in younger patients and false positive results in older patients. For example, 14 beats per minute represents the cut-off of the fifth percentile in 10–29-year-old males and females; 12 beats per minute represents the cut-off of the fifth percentile in 30–39-year-old males and females; 10 beats per minute represents the cut off of the fifth percentile in 40–49-year-old males and females; 9 beats per minute represents the cut-off of the fifth percentile in 50–59-year-old males and females; and 7 beats per minute represents the cut-off of the fifth percentile in 60–59-year-old males and females (Low et al., 1997).

2.1.2. The heart rate response to a Valsalva maneuver

The Valsalva maneuver provides a potential measure of sympathetic, vagal and baroreceptor function; the efferent baroreflex arc consists of sympathetic and parasympathetic pathways. The maneuver is typically performed by blowing through a mouthpiece connected to a mercury manometer for 10–20 s. The mercury column of the manometer is maintained at 40 mm. An expiratory pressure of 40 mmHg appears to result in an optimal response; lower levels do not provide an adequate stimulus while higher levels result in poor reproducibility. There should be a small air leak in the system to prevent closing of the glottis. This test should be repeated several times to ensure a reproducible response.

The hemodynamic response to the resulting sudden, transient increase in intrathoracic and intraabdominal pressure in normal subjects may be subdivided into 4 phases. In phase I, there is a transient rise in blood pressure and a fall in heart-rate that is predominantly due to compression of the aorta and propulsion of blood into the peripheral circulation. The hemodynamic changes during this phase are mainly secondary to mechanical factors and are not accompanied by an increase in muscle sympathetic activity or affected by alpha-adrenergic blockade (Sandroni et al., 1991). Phase II consists of a fall in blood pressure early in phase II with a subsequent recovery of blood pressure in late phase II. These blood pressure changes are accompanied by an increase in heart rate. The fall in cardiac output due to impaired venous return to the heart results in compensatory cardioacceleration and an increase in muscle sympathetic activity and peripheral resistance. In phase III, there is a fall in blood pressure and increase in heart rate that occurs with cessation of expiration due to release of expiratory pressure. Phase IV of the maneuver is characterized by an increase in blood pressure above the baseline value (the overshoot) due to the residual vasoconstriction and now normal venous return. In a pharmacological study of 4 subjects, the blood pressure overshoot in phase IV was significantly decreased by propranolol, unaffected by atropine and enhanced by phentolamine (Sandroni et al., 1991). These results suggest that cardioacceleration plays the central role in the blood pressure overshoot. This blood pressure increase in phase IV is responsible for the baroreflex mediated bradycardia (see Figs. 1 and 2).

The hemodynamic response to the Valsalva maneuver may be attenuated by the buffering effect of blood within the thoracic cavity. Thus, the patient position during, and duration of rest preceding the maneuver significantly affect test results (ten Harkel et al., 1990). In addition, a false positive test may occur in patients with impaired sympathetic nervous system function due to attenuation of the heart rate increase in phase II (van Lieshout et al., 1989).

The heart rate change in response to this maneuver is a widely used indirect, sensitive, specific and reproducible measure of parasympathetic autonomic function. The Valsalva ratio, the ratio of the shortest *RR* interval (the tachycardia) during or after phase II of the maneuver to the longest *RR* interval (the bradycardia) in phase IV of the maneuver, is the most commonly used measure derived from the maneuver. Other statistical measures of the heart rate response to the maneuver include the tachycardia