Chapter 7.2

Heart rate variability

R. Baron\textsuperscript{a,*} and D.J. Ewing\textsuperscript{b}

\textsuperscript{a}Department of Neurology, Christian-Albrechts-University Kiel, Niemannsweg 147, D-24105 Kiel (Germany)
\textsuperscript{b}The Scottish Office Department of Health, St. Andrews House, Edinburgh, EH1 3DG (UK)

Method

Recording of heart rate over long periods using ambulatory ECG monitoring reveals that the heart rate varies continuously, mainly influenced by the cardiac sympathetic and parasympathetic innervation. Therefore, analysis of heart rate variation provides techniques for the investigation of cardiac autonomic innervation. The R-R intervals (inverse of heart rate) yield detailed beat-to-beat information and its variation is the most useful non-invasive index of cardiac autonomic neuropathy (Ewing et al. 1981; Low et al. 1990; Ewing 1993).

Indication

Patients with disorders which might involve damage of the autonomic nervous system should be tested. These include peripheral polyneuropathies caused by diabetes mellitus, alcoholism, chronic renal failure, AIDS, leprosy, the Guillain–Barré syndrome and paraneoplastic neuropathies. Furthermore, central lesions of autonomic centres due to multiple sclerosis or syringomyelia and degenerative disorders of the autonomic nervous system, i.e. primary autonomic failure, also reduce heart rate variability. More recent indications include primary cardiac disorders and the effects of antiarrhythmic drugs on heart rate.

Physiological background

Heart rate variation during normal activity (time-domain technique)

During normal daily activities a beat-by-beat variation in heart rate (or change in the R-R interval length) occurs that is partly determined by the balance between the slowing effect of the autonomic parasympathetic and the accelerating effect of the sympathetic innervation, as well as by humoral mechanisms, and the intrinsic rhythmicity of the cardiac pacemaker tissue. Physiological variations of the heart rate include changes associated with respiration (so-called sinus arrhythmia, 0.15–0.45 Hz), as well as slower alterations associated with blood pressure fluctuations and baroreflex mechanisms (0.1 Hz) and with hormonal changes and thermoregulation (mainly the renin-angiotensin system, 0.05 Hz) and also very slow variations in response to day and night. When subjects are supine, parasympathetic activity is most prominent with only minimal sympathetic activity.

The time-domain technique is only one method of looking at heart rate variability during normal
activity. Alternatively the frequency-domain analysis can be performed but requires much more complicated equipment. Therefore, this chapter will concentrate on the time-domain technique.

Heart rate variation in response to physiological stimuli (cardiovascular reflex tests)

Heart response to deep breathing. During deep respiration the R-R intervals vary in a sinusoidal shape that lengthen during inspiration and shorten during expiration. This variation is greatest at around 6 breaths per minute and is predominantly mediated by parasympathetic cardiac nerves. The response diminishes with age.

Heart rate response to standing up. The heart rate response to standing consists of an immediate and rapid increase, followed by a relative slowing to a level that is usually more rapid than the supine heart rate. In normal subjects the heart rate is maximal at around the 15th beat after starting to stand up, and the relative bradycardia is reached around the 30th beat. Parasympathetic pathways are mainly involved, sympathetic to a lesser extent. The extent of the response diminishes with age.

Heart rate response to the Valsalva manoeuvre. Four phases of the normal cardiovascular response can be distinguished during the Valsalva manoeuvre (blowing against resistance for 10–20 s). Phase I is the immediate onset of strain. This induces a sudden increase in intrathoracic pressure, which is reflected by a brief rise in blood pressure and often a reflex drop in heart rate for 2–3 s. As the strain continues (phase II), venous return is reduced, and this produces a progressive fall in cardiac output and blood pressure. This blood pressure fall results in a steadily increasing heart rate and peripheral vasoconstriction. Phase III is the period immediately following release of strain. The release of intrathoracic pressure and consequent increase in pulmonary venous capacitance leads to a further fall in cardiac output, decrease in blood pressure, and a reflex increase in heart rate for usually 3 or 4 beats. Phase IV consists of a rebound hypertension caused by the increased cardiac output, while systemic vascular resistance is still elevated in response to the falling blood pressure of phase II. This, in turn, produces a reflex bradycardia and peripheral vasodilatation to restore the circulatory haemodynamics to normal. The reflex pathways involved in the Valsalva response are complex. The changes in heart rate are mainly mediated by parasympathetic nerves.

Technical requirements

The time-domain methods to assess resting heart rate variability requires a microprocessor to record the ECG signal and the appropriate program to analyse the R-R interval signal available in most commercial EMG machines. The cardiovascular reflex tests can be performed very easily with minimal equipment. A conventional ECG machine and a pressure gauge attached to a mouthpiece by a tube are needed.

Clinical protocols

Heart rate variation during resting activity (time-domain technique)

A number of different techniques are available to measure heart rate variation (Tables 1 and 2). With the time-domain technique a statistical analysis is applied to a sequence of R-R intervals or R-R

<table>
<thead>
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<th>TABLE 1</th>
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<td>HOW TO REPORT THE RESULTS</td>
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Cardiovascular reflex tests

Deep breathing (E-I) |
| CV or RSMMD |

(deep breathing) |
| Standing up (30:15 ratio) |
| Valsalva ratio |

| Interpretation | Normal Pathologic |
interval differences to measure the variation around the mean. The subject rests for at least for 5 min in a supine position during which the heart rate is recorded continuously using a computer to detect the R wave and save the R-R intervals. The computer program calculates the standard deviation (SD) of the given R-R interval sequence and the coefficient of variation (CV) around the mean R-R interval for that sequence (CV = SD/mean × 100). An alternative approach is to calculate the square root of successive R-R interval differences (RMSDD). A theoretical advantage of this approach is that it is independent of the prevailing heart rate.

Heart rate variation in response to standardized stimuli (cardiovascular reflex tests)

Deep breathing

During the test the subject sits quietly and breathes deeply and evenly at 6 breaths/min (5 s in and 5 s out). The heart rate is continuously recorded. Maximum minus minimum (E-I) R-R interval: The difference between maximal and minimal R-R interval during each 10 s breathing cycle is measured and the mean of the differences during 3 successive breathing cycles gives the maximum minus minimum (E-I) R-R interval. Expiratory to inspiratory ratio (E/I): The maximum and minimum R-R interval during each 10 s breathing cycle is measured. The mean of the maximum-minimum ratio during three successive breathing cycles gives the maximum-minimum (E-I) R-R interval ratio.

If the subject is able to perform the deep breathing task for about 2 min and computer-based equipment is available, CV and RMSDD values can also be calculated according to the descriptions above.

Standing up

The subject is asked to lie quietly on a couch under resting conditions and then to stand up unaided as quickly as practicable and remain standing quietly for 1 min. The longest R-R interval around the 30th beat after standing divided by the shortest R-R interval around the 15th beat is the 30:15 ratio.

Valsalva manoeuvre

The test is performed by asking the subject to sit quietly and then blow into a mouthpiece attached to an aneroid pressure gauge at a pressure of 40 mmHg and to hold the pressure for 15 s. The ratio of the longest R-R interval shortly after the manoeuvre (within about 20 beats) to the shortest R-R interval during or immediately after the strain period (phase II or III) is measured. The result is expressed as the Valsalva ratio (VR) which is taken as the mean ratio from three successive Valsalva manoeuvres.
Applications for clinical practice

Standard battery of tests

It is a false economy to use only one single test of heart rate variation as the repeatability of each test is not perfect. On the other hand several tests described above measure the same stimulus in different ways and give no further information. Therefore, it is recommended to perform a standard battery of tests and calculate several values described above (CV or RMSSD during rest and deep breathing, E-I, 30:15 ratio and Valsalva ratio, see Tables 1 and 2). The heart rate variation should be interpreted as pathologic if more than 50% of the values are abnormal. However, heart rate variation mainly indicates abnormalities that affect the innervation of the heart (parasympathetic cardiac dysfunction). Results should be correlated with other tests of autonomic function which measure different parts of the autonomic nervous system (e.g. blood pressure responses to standing, see Chapter 7.3; sympathetic sudomotor innervation, see Chapter 7.1) in order to classify and quantify the full clinical picture of the autonomic neuropathy.

Factors affecting the quality of the investigation, pitfalls and contraindications

Tests of heart rate variation can only be performed if the subject’s heart is in sinus rhythm. Patients with arrhythmias or ectopic beats must be excluded since otherwise false normal results might be produced. Furthermore, occasional nonsinus, ectopic beats have to be carefully excluded from the analysis. Computer programs to measure successive R-R intervals represent a time-saving approach towards statistical analysis. However, the program must be able to pick up only the R wave and not a tall T wave. Ectopic beats, muscle and movement artefacts must be detected and excluded by the system.

Any medication that affects heart rate may influence the results of the tests.

Analysis of resting heart rate variation includes the danger of overinterpretation of the results. With longer recording periods the variation around the mean becomes more inclusive of general autonomic activity, e.g. humoral factors, as opposed to a specific index of sympathetic and parasympathetic innervation.

During the respiratory stimulus the subject has to be able to breathe deeply and evenly for a period of 2 min since otherwise false pathologic results may occur. Close attention has therefore to be paid that the subject breathes deeply and evenly. Patients with obstructive or restrictive bronchial and lung disease are often unable to perform this respiratory task.

During the ‘standing up’ task a misleading 30:15 ratio may be produced, either if the timing is counted only from when the subject completes the standing up, or if the 15th and 30th beats are adhered to very rigidly, without allowing for slight variations in the speed of the response among individuals. Patients with orthostatic problems due to autonomic neuropathy might be unable to perform the test.

The Valsalva manoeuvre is contraindicated in subjects with obvious clinical cardiac failure, as the baroreflexes are not activated because of the already increased venous return. The blood pressure pattern reflects direct mechanical transmission of the intrathoracic pressure, with no rebound overshoot of blood pressure and an unaltered heart rate. The test is also contraindicated in diabetic patients with proliferative retinopathy because of the possibility of provoking retinal haemorrhage.

References

Ewing, D.J. Noninvasive evaluation of heart rate: the time domain.
Low, P.A., Offer-Gehrking, T.L., Proper, C.J. and Zimmerman, I.