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*For debate . . .*

# Which battery of cardiovascular autonomic function tests?

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Disease of the autonomic nervous system may occur in many medical conditions. Degenerative forms of autonomic neuropathy include primary autonomic failure, Shy-Drager syndrome and Parkinson's Disease with autonomic failure. Autonomic neuropathy may accompany a variety of peripheral neuropathies including Guillain-Barré syndrome, alcoholic neuropathy, porphyria, amyloidosis, poisoning with acrylamide and the rare inherited Riley-Day syndrome (familial dysautonomia). Involvement of the autonomic nervous system may be prominent in acute poliomyelitis and tabes dorsalis. Lesions in the spinal cord (syringomyelia, trauma, tumour) and pontine lesions including infarction, haemorrhage or demyelination can also result in autonomic dysfunction. Autonomic neuropathy is, however, most commonly seen as a complication of diabetes mellitus.

The ubiquitous nature of the autonomic nervous system has allowed tests for its integrity to be described in many systems – cardiovascular, gastrointestinal, urogenital, pupillary, sudomotor and neuroendocrine and these have been reviewed [1, 2]. On the whole, tests in systems other than the cardiovascular are more complex but correlate well with cardiovascular assessments [1]. Although a recently described test of sweating loss in the feet may prove a simple and sensitive test of autonomic denervation [3] and the pupil/iris diameter of the dark adapted pupil (PD%) is a very easily performed test [4], autonomic neuropathy is usually assessed with tests for abnormalities in cardiovascular reflexes.

Disturbance of the autonomic innervation of the cardiovascular system results in a reduction in normal heart rate and blood pressure reflexes. In recent years numerous tests involving quantification of these reflexes have been reported. Even though heart rate abnormalities in association with autonomic neuropathy were recognised in the last century [5], it was really only in the 1960's and 1970's that these specific tests began to be suggested. Tests have been described involving measurement of heart rate or RR interval during the Valsalva manoeuvre [6–8], deep breathing [9–11], normal breathing [12, 13], standing up [14], tilting to upright [15] and over 24 h [16]. Tests have also been described based on blood pressure changes during standing up [17], tilting to upright [15], sustained handgrip [18], and recently deep breathing, Valsalva manoeuvre and a cold pressor test [19].

As far as the heart rate indices are concerned, the reflex changes, or lack of them in disease, have usually been expressed as difference between maximum and minimum heart rate or RR interval during a manoeuvre (max-min difference) or ratio of maximum to minimum (max/min ratio). An attempt was made to simplify the analysis of the RR interval response to standing up (30/15 ratio – see below) [14]. More complicated indices have also been described such as the "acceleration index" [15], "brake index" [15], standard deviation of the RR interval [12, 13] and "mean square successive difference" [13]. Clinicians and research workers have thus had the choice of a bewildering array of possible tests to do for clinical or research purposes.

In 1981 Ewing, Clarke and coworkers from Edinburgh, who deserve considerable credit for having carried out much of the development work of cardiovascular autonomic function tests, adopted a battery of five tests (mean max/min ratio during three Valsalva manoeuvres; mean max-min heart rate difference during six deep breaths; the 30/15 ratio after standing; the systolic blood pressure fall after standing; and the diastolic blood pressure rise during sustained handgrip) with a sixth test (standard deviation of the RR interval during quiet breathing for 5 min) available for research purposes [20]. In a review article in the British Medical Journal in 1982 they proposed the battery of five tests – three predominantly parasympathetic and two predominantly sympathetic – as an assessment of autonomic damage for simple bedside use [21].

Other tests continued to be used and in the 2nd Camillo Golgi lecture, "New horizons for diabetic autonomic neuropathy" to the European Association for the Study of Diabetes in Leipzig in 1987, David Ewing called for uniformity in the tests used. In 1988 the American Diabetes Association in association with the American Academy of Neurology produced a consensus statement

that the heart rate response to the Valsalva manoeuvre, deep breathing and standing and the blood pressure response to standing or tilting and to sustained handgrip had "been validated and shown to be reliable and reproducible, to correlate with each other and with tests of peripheral somatic nerve function, and to have prognostic value" [22]. Increasingly, therefore, tests from the battery of five tests of Ewing and Clarke [21, 23] (Ewing battery) are becoming the norm. The use of such a battery has been considered to allow classification of autonomic neuropathy according to severity – patients being divided into five groups depending on the number of abnormal or borderline results [1].

Nevertheless, there are a number of reasons why a more recently described version of the tests based on the work of O'Brien and colleagues [24] (O'Brien battery) may be preferable. The full Ewing battery of five tests is said to take only about 20 min [21]. However, in practice, particularly by those not doing the tests regularly (as in the ordinary clinical situation), it takes considerably longer. Tests that are quicker and less cumbersome are more likely to be used. In the O'Brien battery only one Valsalva manoeuvre is used rather than three as in the Ewing battery, resulting in a test which is more comfortable for the patient and much quicker. In the O'Brien battery one deep breath instead of six results in an extremely quick test. Although the heart rate changes evoked by a single deep breath in diabetic patients have been shown to be greater than those evoked by repeated breaths [8], a difference in sensitivity of a test involving one breath as opposed to six has not been established. The time taken to measure RR intervals on an ECG strip is conserably less for one breath than six and one Valsalva manoeuvre than three.

The response to standing in the Ewing battery uses the "30/15 ratio". However, the minimum RR interval only approximates to the 15th RR interval and the maximum only approximates to the 30th and there is considerable individual variation [25]. Inevitably, therefore, the ratio of the 30th to the 15th RR interval after standing underestimates the max/min ratio, as has been demonstrated [25], Indeed O'Brien and colleagues found that from 294 normal subjects, 43% had a 30th to 15th ratio less than unity [24]. Strictly the 30/15 ratio takes the shortest RR interval "at or around" the 15th beat and the longest "at or around" the 30th beat [21]. The result will obviously depend on how far "around" the 15th and 30th beats the net is cast, the 30/15 ratio becoming the max/min ratio if the net is cast wide enough every time.

Another important consideration as regards test sensitivity is the accuracy of the normal range used. It is now well recognised that the normal response to the heart rate tests varies with age [25–28]. The tests of the Ewing battery, which were developed with their normal ranges before this was appreciated, have only one normal range each regardless of age [21, 23]. Thus, they stand to generate false negative results among younger patients and false positive results among the older age group. The O'Brien battery uses age-related normal ranges based on 310 healthy subjects age 18–85 years [24].

The O'Brien battery has other subtle advantages. For the heart rate and blood pressure responses to change in posture from lying to standing, in the Ewing battery the timing of the test starts as the patient begins to move in the process of standing up [14, 21]. Whether the response is monitored using an ECG machine, or a computer, this easily results in considerable artifact formation which is avoided if the ECG assessment starts as the patient attains the upright posture as in the O'Brien version. For the Valsalva, Ewing takes shortest during and longest after that manoeuvre [21, 23]. Experience with the Valsalva test reveals that in the normal subject the RR interval continues to shorten for several seconds after the Valsalva manoeuvre finishes before it starts to lengthen. For his test and normal range O'Brien looked in those seconds beyond the end of the Valsalva manoeuvre to see if the shortest occurred there and, if it did, this was the one used. Hence, the O'Brien Valsalva test is, for another reason, potentially a more sensitive assessment.

Thus, there are several reasons why, instead of the battery of tests proposed by Ewing and Clarke [21, 23], a battery based on O'Brien and colleagues [24] may make a preferable norm. This battery of tests could be 1) max-min heart rate difference during a single deep breath 2) Valsalva ratio based on a single Valsalva manoeuvre (taking the shortest RR interval during or just after the manoeuvre); 3) max/min ratio after standing up. Age-related normal ranges would be used for these three tests [24]. 4) The systolic fall after standing would remain as a fourth test. Computer-assisted systems to collect and analyse the heart rate data and handle the blood pressure data for all the tests discussed, are becoming more readily obtainable (eg RR Medical Electronics Ltd., 11 York Place, Leeds, UK). 5) If such a system is available, the standard deviation of the RR interval during quiet breathing while resting supine is easily assessed as a fifth test, again using an age-related normal range [24]. 6) The diastolic blood pressure rise after sustained handgrip as described by Ewing and colleagues [18], which may assess predominantly sympathetic innervation [21], could remain as a further test if a handgrip dynamometer is available (eg Tephcotronics Ltd., 5, Hillview Dr., Edinburgh, UK). This battery of tests would be quicker, easier to perform and more comfortable for the patient, and with its age-related normal ranges may be more sensitive to detect abnormality with fewer false results than the battery of Ewing and Clarke [21]. Such a possibility warrants further consideration before the latter battery becomes accepted as the norm.

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