EDITORIAL REVIEW

Cardiovascular reflexes and autonomic neuropathy

D. J. EWING

University Department of Medicine, The Royal Infirmary, Edinburgh, Scotland

Introduction

Clinical features of autonomic neuropathy include postural hypotension, sweating abnormalities, disturbance of body temperature regulation, gastric fullness and nausea, intermittent nocturnal diarrhoea, constipation, bladder problems and impotence. In diabetic patients, gustatory sweating and hypoglycaemic unawareness also sometimes occur (Johnson & Spalding, 1974). The onset of symptoms is usually insidious and permanent, but may occasionally be acute and reversible (Young, Asbury, Corbett & Adams, 1975). Autonomic dysfunction can arise from three main causes: first, those where the damage to the autonomic nervous system is isolated, as in primary postural hypotension (Bannister, Sever & Gross, 1977) and familial dysautonomia (Brunt & McKusick, 1970); secondly, those caused by toxic or pharmacological agents which interfere with autonomic reflexes; thirdly, those associated with systemic disease, of which diabetes mellitus is the most common. Other diseases which may cause autonomic dysfunction include amyloidosis, porphyria, tetanus, polyneuritis, tabes dorsalis, parkinsonism, chronic renal failure and alcoholism, and occasionally autonomic neuropathy has been associated with carcinoma of the bronchus or the pancreas (Johnson & Spalding, 1974).

Although it is possible to localize lesions within the autonomic nervous system to afferent or efferent sympathetic or parasympathetic pathways (Johnson & Spalding, 1974; Moskowitz, 1977), many of the available tests are complex and invasive and often lack adequate control measurements (Young et al., 1975). Because of the patchy nature of autonomic neuropathy, current interest has centred around the search for bedside tests that are 'global', reproducible and non-invasive. This review summarizes the present state of knowledge of simple tests of cardiovascular reflex function in the clinical evaluation of autonomic neuropathy, particularly in diabetic subjects.

Cardiovascular reflexes

Heart rate control

Neural control of the heart is extremely complex and has been reviewed in detail elsewhere (Levy, 1971; Higgins, Vatner & Braunwald, 1973; Kent & Cooper, 1974). The concept of 'intrinsic heart rate' has been developed by Jose & Collison (1970) to describe a heart pharmacologically denervated with atropine and propranolol. This results in a moderate tachycardia, which does not vary in response to stimuli that would normally influence heart rate reflexly. A surgically denervated heart responds in a similar fashion (Shaver, Leon, Gray, Leonard & Bahnson, 1969). In 11 healthy young subjects at rest, the mean heart rate increased from 70 beats/min to 132 beats/min with 2 mg of atropine intravenously, and slowed to 111 beats/min when intravenous propranolol (10 mg) was added. Propranolol alone lowered the heart rate to 58 beats/min (Leon, Shaver & Leonard, 1970). Diabetic subjects with neuropathy have been found to have fixed resting heart rates that are similar to the intrinsic heart rate of normal subjects and diabetic subjects without neuropathy (Kaldor, Gachalyi, Szigeti & Szilagyi, 1977). Pharmacological denervation with atropine and propranolol in diabetic subjects with clinical features of autonomic neuropathy results in very small changes in heart rate (Lloyd-Mostyn & Watkins, 1975). Resting tachycardia has been suggested as a possible marker of autonomic dysfunction, as it has been found occasionally in diabetic subjects with clinical features of autonomic neuropathy (Martin, 1953; Keen, 1959; Page & Watkins, 1977). In porphyria complicated by neuropathy, and in polyneuritis, a tachycardia has been noted which...
disappeared as the neuropathy improved, and this was thought to be due to autonomic cardiac involvement, although no detailed tests were used to confirm this (Ridley, Hierons & Cavanagh, 1968). Diabetic subjects, as a group, have a higher mean heart rate when compared with age- and sex-matched normal control subjects (Ewing, Irving, Kerr, Wildsmith & Clarke, 1974), but the significance of this observation is unknown.

**Beat-to-beat variation in heart rate**

Cyclical variations in heart rate, including sinus arrhythmia, are well recognized (Davis & Neilson, 1967). Beat-to-beat variation in heart rate is most marked at slow heart rates and with deep breathing (Wheeler & Watkins, 1973), particularly at a frequency of about 6 breaths/min. The variation is diminished by faster heart rates, with cardiac failure, in subjects with cerebral catastrophes and in older subjects (Wheeler & Watkins, 1973; Vallbona, Cardus, Spenser & Hoff, 1965). Beat-to-beat variation is abolished by cutting the vagus nerve in animals (Samaan, 1935), and in man by giving atropine, whereas propranolol does not affect it (Wheeler & Watkins, 1973). A surgically denervated heart beats at a fixed rate (Shaver et al., 1969). Beat-to-beat variation of heart rate is thus under parasympathetic control.

Wheeler & Watkins (1973) showed that diabetic subjects with autonomic neuropathy had a marked reduction, or even absence, of beat-to-beat variation when compared with control subjects, and this observation has been confirmed by others (Bennett, Hosking & Hampton, 1975; Morley, Asvat, Klein & Lowenthal, 1977). Reduced variation in heart rate has also been demonstrated in diabetic subjects who had no features of autonomic neuropathy (Murray, Ewing, Campbell, Neilson & Clarke, 1975; Gundersen & Neubauer, 1977), and also after ketoacidosis (Campbell, Fraser, Ewing, Baldwa, Harrower, Murray, Neilson & Clarke, 1976), and even at first diagnosis (Fraser, Campbell, Ewing, Murray, Neilson & Clarke, 1977). Heart rate variation has not been described in other forms of autonomic neuropathy. In diabetic subjects therefore, vagal damage, as instanced by reduced beat-to-beat variation, can be demonstrated to occur more widely than would be expected from the symptoms of autonomic neuropathy.

Three methods of measuring and analysing beat-to-beat variation have been described. In the first (Wheeler & Watkins, 1973) an instantaneous heart rate meter is used to measure the differences between the maximum and minimum heart rates over 1 min when breathing deeply at 6–8 breaths/min. Normal subjects under 50 years old showed differences of more than 15 beats/min, whereas all but two of 47 subjects with autonomic neuropathy had differences of less than this (Page & Watkins, 1977).

A second method (Murray et al., 1975) involves recording the ECG on to magnetic tape over 5 min when standing and breathing quietly, the standard deviation of the mean R–R interval over that period being used as a measure of beat-to-beat variation. Although background autonomic activity may occur when standing (Gundersen & Neubauer, 1977), in three normal subjects intravenous atropine reduced the beat-to-beat variation from 47 to 13 ms, whereas propranolol had no effect. However, this technique does not separate normal subjects from abnormal subjects as well as previously thought. In 10 young normal subjects, measurements of beat-to-beat variation were repeated ten times, revealing a wide range in individual responses, many readings falling below the previously defined normal lower limit (Fig. 1). Gross abnormalities of autonomic function can nevertheless be revealed with this method (Fig. 2), but it cannot be used to quantify different degrees of autonomic neuropathy. Bennett, Fentem, Fitton, Hampton, Hosking & Rigott (1977) compared the results by the first method (Wheeler & Watkins, 1973) with those of the second and concluded that
the former method, which relies on respiratory variation, was the more reliable. However, these authors did not define their normal values and the age of the diabetic patients was not considered.

A third method (Gundersen & Neubauer, 1977) records an ECG strip of 150 consecutive beats while the subject is lying quietly. Each R-R interval is measured, and the mean of the squares of differences between successive intervals, the 'mean square successive difference', is used to give a measure of beat-to-beat variation.

These methods of measuring beat-to-beat variation are objective and easily made, but they suffer from poor reproducibility and wide scatter in normal values. Short-term beat-to-beat variability, however, compares closely with heart rate variability measured from a 24-h ECG tape (Bennett, Riggott, Hosking & Hampton, 1976), and it is probably not possible further to simplify the measurements. Baldwa & Ewing (1977) found that the difference between the longest and shortest R-R interval in a short ECG strip could serve to exclude cardiac vagal damage in the absence of more sophisticated equipment, but could not be used for diagnosis of cardiac vagal damage.

Valsalva manoeuvre

During the Valsalva manoeuvre (forced expiration against resistance) the reflex events include a tachycardia and peripheral vasoconstriction during strain, followed after release by an overshoot in blood pressure and a bradycardia (Sharpey-Schafer, 1965). Pharmacological blocking experiments, both in dogs and man, have confirmed the reflex nature of these changes. The heart rate responses can be abolished by parasympathetic blockade with atropine (Leon et al., 1970) but not with cardiac sympathetic blockade (Spodick, Meyer & Quarry-Pigott, 1974), whereas the blood pressure overshoot can only be abolished by total autonomic and cardiac sympathetic blockade (Sarnoff, Hardenbergh & Whittenberger, 1948; Bunnell, Greene & Kunz, 1951; Cudkowicz, 1968; Korner, Tonkin & Uther, 1976). A 'square wave' response occurs in subjects with clinically evident cardiac failure (Sharpey-Schafer, 1955), whereas in subjects with absent circulatory reflexes there is a steadily falling blood pressure during strain, a slow return to normal pressure after release and no change in heart rate during or after strain (Sharpey-Schafer, 1956).

The intra-arterial blood pressure measurements during and after the Valsalva manoeuvre have been widely used to assess disordered autonomic function in different conditions (Sharpey-Schafer & Taylor, 1960; Watson, 1962; Appenzeller & Descarries, 1964; Mason, Kopin & Braunwald, 1966; Gross, 1970; Bannister et al., 1977). Although the response has usually been assessed by relating the increase in diastolic blood pressure after strain to the decrease in pulse pressure during strain (Sharpey-Schafer, 1955), this has recently been found to be less reliable than previously thought (Johnson & Spalding, 1974). The heart rate changes during and after the Valsalva manoeuvre have been found to be a reliable guide to the associated haemodynamic events (Elisberg, 1963). Levin (1966) defined the 'Valsalva ratio' as the ratio of the longest R-R interval after the manoeuvre to the shortest R-R interval during the manoeuvre. Although this ratio does not separate the different heart rate components, it has nevertheless provided a useful method of examining the Valsalva manoeuvre. The normal Valsalva ratio is 1·50 or greater (Levin, 1966), but a lower limit of 1·20 has recently been proposed (Ewing, Campbell, Burt & Clarke, 1973; Bhatia, Sainani, Nayak & Diwate, 1976). The Valsalva ratio is reproducible in normal subjects though it declines with age (Levin, 1966; Baldwa & Ewing, 1977).

An abnormal response to the Valsalva manoeuvre is quite common in diabetic subjects and had been assessed non-invasively in several studies.
Of 337 consecutive clinic diabetic patients, 20% had an abnormal response, judged by feeling the pulse (Sharpey-Schafer & Taylor, 1960). Others, using an ECG, have found that impaired responses correlated well with peripheral neuropathy, and some of these patients had symptoms of autonomic neuropathy (Nathanielsz & Ross, 1967; Bishnu & Berenyi, 1971). Low Valsalva ratios have been found in diabetic subjects with clinical features of autonomic neuropathy (Ewing et al., 1973; Low, Walsh, Huang & McLeod, 1975; Bhatia et al., 1976; Morley et al., 1977). Subjects with impotence alone, however, had more normal Valsalva ratios, suggesting that impotence can only be reliably attributed to autonomic neuropathy when it is associated with other features of the disorder (Ewing et al., 1973).

**Posture**

Standing up involves the integration of a number of cardiovascular reflexes. There is immediate pooling of blood in the lower extremities with a consequent fall in blood pressure, but provided that the baroreflexes are functioning normally, this is rapidly corrected by peripheral vasoconstriction and a tachycardia (Hellebrandt & Fransen, 1943; Currens, 1948; Wagner, 1959). Postural hypotension can result from damage to any part of the baroreflex arc and the mechanisms responsible have been reviewed (Johnson & Spalding, 1974; Johnson, 1976). Defective postural responses also occur in some elderly subjects (Johnson, Smith, Spalding & Woolner, 1965; Caird, Andrews & Kennedy, 1973). In diabetic subjects postural hypotension was first clearly delineated as a feature of autonomic damage by Rundles (1945) and has been found subsequently in many diabetic patients with symptoms suggestive of autonomic neuropathy (Berner, 1952; Odel, Roth & Keating, 1955; Frank, Frewin, Robinson & Wise, 1972; Ewing et al., 1973; Christlieb, Munichoodappa & Braarten, 1974; Bennett et al., 1975; Low et al., 1975; Morley et al., 1977). Insulin may also contribute to the severity of the postural hypotension since it is thought to cause a slight reduction in plasma volume (Gundersen & Christensen, 1977) and cardiac filling pressure (Miles & Hayter, 1968). When the compensatory baroreflex mechanisms are inoperative, as in autonomic neuropathy, insulin aggravates the postural hypotension (Page & Watkins, 1976), but this may be reduced by changing the timing of insulin injections (Palmer, Perkins & Smith, 1977).

Most previous work on postural changes has used a tilt-table and relatively little attention has been paid to the heart rate changes. However, it has recently been shown that in normal subjects there is a characteristic and consistent immediate heart rate response to standing, tachycardia being maximal around the fifteenth beat after standing, and a relative bradycardia maximal around the thirtieth beat. Intravenous atropine abolishes this response, whereas propranolol does not affect it, suggesting that the normal heart rate response to standing is mediated by the vagus. As might be expected, diabetic subjects with autonomic neuropathy had an abnormally flat response (Ewing, Campbell, Murray, Neilson & Clarke, 1978). It has been suggested that different categories of cardiovascular reflex defects can be distinguished by relating the blood pressure and heart rate changes on standing after 15 s, 1 min and 5 min (Bennett et al., 1975). Unless, however, the whole immediate heart rate response is considered, this approach could lead to error.

The immediate heart response to standing has provided the basis for a further simple objective test of cardiovascular reflex activity. The R–R intervals at beats 15 and 30 after standing are measured from an ECG strip, and the ‘30/15 ratio’ is determined. This is reproducible and does not depend on age or the resting heart rate in normal subjects, where values are greater than 1.03, whereas in diabetic subjects with autonomic neuropathy values are usually 1.00 or less (Ewing et al., 1978).

**Sustained muscular exercise**

During sustained isometric muscular exercise, as for example during sustained handgrip, there is normally a heart rate-dependent increase in cardiac output with no change in peripheral vascular resistance and a consequent increase in systemic blood pressure (Lind, Taylor, Humphreys, Kennedy & Donald, 1964). The initial heart rate rise is due to vagal withdrawal (Freysschuss, 1970; Borst, Hollander & Bouman, 1972), but if this is inoperative, increased cardiac sympathetic stimulation may occur to give a tachycardia (Martin, Shaver, Leon, Thomson, Reddy & Leonard, 1974), and the blood pressure can also be increased by peripheral vasoconstriction (MacDonald, Sapru, Taylor & Donald, 1966).

An abnormally small blood pressure increase during sustained handgrip has been found in some unselected diabetic subjects (Ewing et al., 1974), in diabetic subjects with autonomic neuropathy (Ew-
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In patients with chronic renal failure (Ewing & Winney, 1975). Diabetic subjects have also been found to have reduced heart rate responses (Nazir, Taton, Chwalbinska-Moneta & Brzezinska, 1975). The blood pressure response to a standardized sustained handgrip at 30% of the maximum voluntary contraction has been suggested as a further non-invasive test of autonomic function. A rise of less than 15 mmHg of diastolic blood pressure during handgrip is abnormal (Ewing et al., 1974), and implies extensive damage to the autonomic pathways mediating the cardiovascular responses.

Other cardiovascular reflexes

A number of other tests of cardiovascular reflex function have been described, the arterial blood pressure response to different stresses including mental calculation, loud noise, ice and lower-body negative pressure being used (Johnson & Spalding, 1974; Bannister et al., 1977). These require intra-arterial cannulation for accurate assessment and some reports lack adequate control data.

The heart response to changes in blood pressure induced by drugs such as phenylephrine or nitroglycerine has been used to measure baroreceptor function (Smyth, Sleight & Pickering, 1969), and these methods have also been applied to disordered autonomic function in diabetic patients (Low et al., 1975; Bennett, Hosking & Hampton, 1976).

Clinical relevance of abnormal cardiovascular reflexes in diabetic subjects

In diabetic subjects the clinical importance of abnormal cardiovascular reflexes is gradually being unravelled. Abnormal cardiovascular reflexes, associated with clinical symptoms of autonomic neuropathy, carry a poor prognosis. Of 37 patients followed for 2\(\frac{1}{2}\) years, 50% of those with abnormal cardiovascular reflexes died within that period (Ewing, Campbell & Clarke, 1976) although it was not possible to say that autonomic neuropathy *per se* caused the deaths.

One possible factor that might be relevant to this high mortality has been suggested by a recent report of 12 unexplained cardiorespiratory arrests in diabetic subjects with autonomic neuropathy (Page & Watkins, 1978). Experimentally, the ventilatory responses to hypoxia can be diminished by vagal blockade (Phillipson, Hickey, Bainton & Nadel, 1970) and by carotid body denervation (Lugliani, Whipp, Seard & Wasserman, 1971). Patients with familial dysautonomia may have a diminished sensitivity of their respiratory centre to carbon dioxide and a defective hypoxic ventilatory response to steady-state hypoxia (Filler, Smith, Stone & Dancis, 1965; Edelman, Cherniack, Lahriri, Richards & Fishman, 1970). One diabetic and several patients with tabes dorsalis have also been found to have an abnormal response to hypoxia (Evans, Benson & Hughes, 1971). It is possible therefore that damage to respiratory reflexes in diabetic autonomic neuropathy may help to explain these cardiorespiratory 'events'. Furthermore if diabetic subjects with autonomic neuropathy do have a diminished hypoxic drive to ventilation this could have clinical implications in anaesthesia and respiratory disease.

Conclusion

Autonomic neuropathy can now be simply assessed at the bedside by several non-invasive tests of cardiovascular reflex function, including beat-to-beat variation in heart rate, the responses to the Valsalva manoeuvre and sustained handgrip, the postural fall in blood pressure and the immediate heart rate response to standing. Abnormalities of these tests, in association with clinical features suggestive of autonomic neuropathy, carry a poor prognosis in diabetic subjects. The usefulness of these tests in other conditions is, as yet, largely unknown.

It is now becoming increasingly apparent that as more aspects of autonomic dysfunction are studied, so more and more defects are being uncovered. We are only just now beginning to piece together some of the relationships between the physiological abnormalities and their clinical relevance, but much further work is needed to fully understand the role of the autonomic nervous system in disease.

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