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DIABETIC AUTONOMIC NEUROPATHY: CONVENTIONAL CARDIOVASCULAR LABORATORY TESTING AND NEW DEVELOPMENTS

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SUMMARY

Cardiovascular reflex tests remain the investigational cornerstone for the assessment of patients in the clinical autonomic laboratory. Three cardiovagal tests have been found suitable for testing: the instantaneous heart rate responses induced by deep breathing, Valsalva's manoeuvre and standing up. Suitable laboratory indices of adrenergic function include continuous monitoring of blood pressure responses induced by Valsalva's manoeuvre and standing up, which is now possible through tracking of beat-to-beat blood pressure changes at the finger. Spectral analysis of heart rate and blood pressure and pulse wave analysis for stroke volume changes are promising approaches to evaluate abnormalities in arterial baroreflex regulatory mechanisms in diabetic patients.

Key words: Diabetes mellitus, autonomic nervous system, blood pressure, heart rate variability, baroreceptors, power spectrum analysis.

INTRODUCTION

A remark by the obstetrician dr. T Wheeler to the diabetologist dr. PJ Watkins in 1972 that loss of heart rate variation in the fetus in utero might be due to hypoxia of central autonomic centres, sparked off the thought to use a fetal heart rate monitor to assess whether beat-to-beat variability in heart rate was altered in diabetic patients with neuropathy. An abnormal reduction and even total loss in beat-to-beat heart rate variability was documented and clinical attention was drawn to the key role played by the vagus nerve in the mediation of heart rate variability [1,2]. Following this important report, the field of autonomic cardiovascular dysfunction in diabetes has developed rapidly in the period 1975-1985. Bennnett et al. investigated the physiological mechanisms underlying the impairment in heart rate variability and provided the basis of our understanding of the cardiovascular pathophysiology involved [3]. The value of cardiovascular function tests to study the natural history of autonomic dysfunction in diabetic patients was demonstrated by Ewing et al. [4] and abnormalities in sympathetic function were detailed by Hilsted et al. [5]. Many reports have been published since and the availability of microcomputers has resulted in heart rate variability measures of increasing complexity. Two approaches are now commonly applied: 1) measurement of background heart rate variability over time periods ranging from minutes to hours and using time-domain and frequency-domain

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methods for the analysis 2) measurement of beat-to-beat heart rate changes in the clinical laboratory in response to known stressors like deep breathing, standing and straining [6-8]. This short review covers the second approach. It focuses on the developments in the last 10 years.

PHYSIOLOGICAL BACKGROUND

Heart rate variability is mainly a reflection of the influence of the autonomic nervous system on the sinus node of the heart. The heart rate alters with many of the demands on the cardiovascular system that relate to changes in respiration, straining, posture and physical or mental activity. From the many reflexes that stabilize blood pressure, the arterial baroreflex is the most relevant in cardiovascular function testing, since it is fast acting. For the purposes of the following discussion we have simplified the assessment of neural reflex control of systemic blood pressure by assuming that the arterial baroreceptor reflex is solely responsible for circulatory homeostasis. To regulate beat-to-beat blood pressure the arterial baroreflex has three levers to operate: rate and contractility of the heart, systemic vascular resistance and venous capacitance. The efferent limbs of the baroreflex arc consist of sympathetic and parasympathetic fibres to the heart as well as sympathetic fibres to the smooth muscles in the peripheral blood vessels. Modulation of vagus nerve activity permits the heart rate to change within one second. Sympathetically mediated changes in heart rate, cardiac contractility and arteriolar vasomotor tone need 2-3 seconds to begin [9,10]. Direct information about the function of the sympathetic nervous system in humans is provided by microneurographic recordings of postganglionic sympathetic nerve firing rates (in humans only to skeletal muscle and skin) and by measuring rates of organ-specific noradrenaline spillover to plasma by radiotracer methodology. These techniques are research tools, which measure different aspects of sympathetic nervous function. Vagal neural activity cannot be measured directly in humans. Selective methods used to investigate human arterial baroreflex function include either bolus injections of vasoactive drugs such as phenylephrine or nitroprusside to raise or lower blood pressure, or neck suction or compression to affect carotid sinus baroreceptors. These interventions provide important information, but are less easily applied in routine clinical use [9,10]. In the clinic assessment of cardiovascular control is based on an analysis of heart rate and blood pressure responses to physiological stressors like deep breathing, standing and straining. This "simple" approach provides valuable information about the presence or absence of functional disturbances in the regulatory capacity of the autonomic nervous system.

CARDIOVASCULAR REFLEX TESTING

A cardiovascular laboratory test should relate to known physiological functions and be clinically relevant. The potential to distinguish between normal and abnormal function and good long-term within-subject repeatability are other important prerequisites. Additional requirements are the applicability of the manoeuvres involved and the availability of age- related reference values for the circulatory responses evoked

[9-11].

In the report and recommendations of the San Antonio Consensus Conference on diabetic neuropathy in 1988 it was agreed that five simple non-invasive tests were most useful to study cardiovascular reflex activity [12]. Three tests, the heart rate responses to the Valsalva manoeuvre, deep breathing and standing up, are based on beat-to-beat measurement of heart rate changes, while the other two tests, the responses to blood pressure response to standing and sustained handgrip, depend on conventional indirect blood pressure measurements with cuff and stethoscope. Additional stressors like tilting, coughing, squatting and apnoeic face immersion have been proposed from time to time, but advantages of these tests have never been demonstrated [9,11].

New techniques have become available since 1988. Finapres, a device capable of tracking blood pressure changes non-invasively and continuously at the finger has importantly enhanced laboratory evaluation of cardiovascular reflex control [9-11,13,14]. Power spectral analysis of heart rate and blood pressure variability has become a tool to explore neural regulatory mechanisms [15,16]. A novel development is the calculation of beat-to-beat changes in stroke volume with pulse contour algorithms and model simulation [17,18]. The conventional cardiovascular reflex tests and the possible contributions of the new developments will now be considered.

CONVENTIONAL ASSESSMENT

The assessment of cardiovascular autonomic nerve damage from the combined results of the five conventional tests has been propagated by Ewing [4] and still forms the core of the cardiovascular autonomic evaluation performed by many autonomic laboratories [7]. However, at present, almost ten years after the San Antonio Consensus conference, confounding variables in the conventional battery have been identified and suggestions for improvement have been brought forward [19-21].

A clinical autonomic testing report of the therapeutics and technology assessment subcommittee of the American Academy of Neurology recently came with a new proposal [22]. It recommends to assess separately the cardiovagal system, the adrenergic system and the sudomotor system, depending on the clinical question and the particular aspect of the autonomic nervous system that require testing. The recommendations of the report for the assessment of cardiovascular reflexes are in good agreement, though not identical with current practice in Europe [9].

CARDIOVAGAL TESTS

Three cardiovagal tests were found to have high sensitivity, specificity and long-term reproducibility, and therefore suitable for clinical autonomic laboratory testing: the instantaneous heart rate changes induced by deep breathing, Valsalva's manoeuvre and standing up [22]. The report does not give specific recommendations on how to quantify the cardiovagal responses [for review see 7]. The measurement in

RR-intervals appears to be more physiological, since it more directly reflects cardiac autonomic outflow [10,23]. In addition, the sensitivity of measures in R-R intervals is expected to be greater [23]. Normal values depend on patient age, but standards for R-R intervals are not yet available. The same is true for longitudinal follow-up in a large population of diabetic patients. In practice differences between measurement in RR-interval or heart rate hardly ever will cause problems in interpretation [9].

The long-term experience in autonomic laboratories is obtained with the measurements of cardiovagal function in heart rate or dimensionless ratios. These two measures are well validated and age related reference values are available [11,20,24]. Measurements in ratios, however, do not relate to a clear physiological function, are greatly influenced by resting tachycardia and do not allow to distinguish between normal and abnormal cardiovagal control in elderly subjects. They are thus better avoided [11,20].

The initial heart rate response on standing has been quantified by the peak initial heart rate increase and/or the magnitude of the reflex bradycardia [9]. Ewing expressed the relative bradycardia originally as the ratio between the thirtieth and fifteenth R-R interval after the onset of standing, the 30/15 ratio. Indeed, on average, the maximal heart rate increase is reached at around beat 15 and the relative bradycardia at around beat 30. However, since there are considerable interindividual differences, measurement of the 30/15 ratio at exactly beats 30 and 15 underestimates the true RRmax/RRmin ratio. Clinical autonomic laboratories using this measure now recommend to use the highest and lowest heart rate in the first 30 s from the onset of standing and to quantify the relative bradycardia as HRmax/HRmin ratio [21,24,25]. The reflex bradycardia upon standing is dependent on sympathetically mediated vasoconstriction. Thus it can be applied only as an index of cardiovagal function if sympathetic vasomotor innervation is intact [19]. In addition, as mentioned above, the test range for the HRmax/HRmin ratio does not distinguish between normal and abnormal heart rate control in elderly subjects [20]. We, therefore, prefer the use of the initial peak heart rate increase on standing (HRmax) to assess instantaneous heart rate control [9]. Confounding variables of this measure are well known, the test range is sufficient also in the elderly, and its long-term within-subject repeatability is high [9,19,20,26].

The heart rate response to deep breathing (I-E difference) is a sensitive laboratory measure to assess vagal heart-rate control [9]. We have found the combination of abnormally low test scores for both the I-E difference and HRmax to standing eminently suited to identify definite cardiac vagal neuropathy in individual patients [9]. HRmax/HRmin ratios induced by standing and the Valsalva ratios are in these conditions, in our experience, abnormally small as well.

Finapres can be applied to estimate baroreceptor-cardiac reflex sensitivity [10]. Two methods have been described: a) measuring the change in interbeat interval per unit change in blood pressure (ms/mmHg) induced by Valsalva's manoeuvre or by standing up and b) sequence analysis [10,27-29]. Baroreflex sensitivity was found to be reduced in a recent study in a group of adult insulin dependent diabetic patients who had no long-term complications and had normal scores for the conventional laboratory tests for autonomic function [29]. The authors argued that this technique should become a standard test for detecting early autonomic dysfunction in diabetic patients. This interesting observation deserves further evaluation.

LABORATORY TESTS OF ADRENERGIC FUNCTION

Finapres has permitted to analyse the transient changes in blood pressure induced by Valsalva's manoeuvre and standing up in the clinical autonomic laboratory [9,19,30-32]. A quantitative analysis of the individual phases of Valsalva's manoeuvre has been reported to provide a sensitive index of adrenergic function [30,31] and this method is recommended in the assessment report of the American Academy of Neurology [22]. Recent studies in diabetic patients convincingly show that by using this approach early impairment of adrenergic function is indeed identified both during Valsalva's manoeuvre and standing up tests [33,34]. Orthostatic stress testing can be used to evaluate both instantaneous- and prolonged orthostatic circulatory responses. Beat-to-beat blood pressure and heart rate recordings have greatly enhanced our understanding of the spectrum of normal and abnormal responses [9,32] and Finapres is now considered the method of choice during orthostatic stress testing in the laboratory [22,35].

Placing one hand in ice cold water, mental stress and isometric exercise such as sustained handgrip, result in increased systemic blood pressure. The afferent pathways involved in these stresses (pain, central command, muscle receptors) are distinct from the afferent pathways of the arterial baroreflex. In subjects with disturbed control of systemic blood pressure during orthostatic stress or Valsalva straining, a rise in blood pressure in response to these stressors suggests that efferent sympathetic pathways are still functional [9,11]. However, the experience with confounding variables in these tests is less than with the cardiovagal tests [11]. In addition, sustained handgrip has consistently been found of limited sensitivity and specificity [20,21]. The assessment report of the American Academy of Neurology recommends to consider this method as investigational [22]. The report does not consider any other tests. In our experience placing one hand in ice cold water is the most useful physiological stressor to test the function of efferent sympathetic pathways [9].

NEW DEVELOPMENTS

Spectral analysis of heart rate and blood pressure allows biological interpretation of circulatory rhythms. This technique is increasingly used to evaluate autonomic regulatory mechanisms in diabetic subjects both for short-lasting recordings under standardized laboratory conditions and 24 hours recordings under daily life conditions [for review see 36]. A close correlation between spectral analysis measures of heart rate and the conventional measurements was demonstrated indicating the ability of this technique to reflect the occurrence of alterations in autonomic cardiovascular control [36,37]. Several reports have documented that spectral analysis of heart rate and blood pressure provides a more sensitive estimate of specific alterations in short-term cardiovascular control than the conventional techniques [29,38,39]. The minimal patient cooperation needed to carry out spectral analysis and the possibility of deriving indexes of both sympathetic and parasympathetic nervous system functions, have been brought forward as important advantages of this laboratory technique.

Availability of techniques for combined beat-to-beat recording of blood pressure and heart rate signals allows our evaluation of autonomic dysfunction under daily life conditions throughout the 24 hours, out of the somewhat artificial environment of the cardiovascular laboratory [36]. However, several issues need to be resolved before spectral analysis techniques can be advocated in the assessment of cardiovascular control in individual patients in the laboratory [36,40]. First, spectral analysis has been shown to be a sensitive estimate when groups of patients and controls were compared. It is, however, unclear at this point, whether impaired control in individual patients can be identified. Age related reference values for heart rate and blood pressure spectral powers are clearly needed. Second, of great importance in testing for autonomic neuropathy is long-term (after weeks to months) reproducibility in individual patients, but long-term reproducibility performed in large groups of healthy subjects and patients has not been tested for spectral techniques [36,40]. Finally and importantly, the clinical relevance of the search for sensitive estimates of alterations in short-term cardiovascular control needs to be considered. A sensitive test is used to screen patients for an abnormality and screening is only indicated in case of efficacious treatments for the primary disease and/or efficacious preventive manoeuvres for its sequelae. Early detection of subclinical diabetic autonomic dysfunction has been suggested to be important for risk stratification and subsequent management [8]. However, at this moment there is neither efficacious treatment for diabetic autonomic dysfunction nor for the associated increase in sudden death. Large-scale screening for impairment of short-term cardiovascular control is, therefore, not yet indicated.

Another new development is pulse wave analysis. It enables the clinician to observe beat-to-beat changes in stroke volume derived from the arterial pulse wave [17,18]. Pulse wave analysis can also be applied to the finger arterial wave and enables to evaluate the hemodynamics underlying changes in blood pressure during orthostatic stress testing [41]. Pulse wave analysis opens new fields of investigation both under laboratory and ambulatory conditions [38-40]. This approach has not yet been applied to diabetic patients. Recently, solutions for the drawbacks of peripheral finger blood pressure measurements have been described. Finally, reconstruction of brachial artery pressure waves from finger measurements by correction for pulse wave distortion and individual pressures gradients pressure has been found feasible and reliable [45]. The availability of optimally corrected finger pressure measurements will be especially helpful during experiments that require continuous knowledge of the exact blood pressure level and in circumstances in which finger pressure measurements have been shown to represent brachial artery pressure with reduced accuracy.

CONCLUSION

Noninvasive continuous monitoring of finger blood pressure has significantly furthered physiological understanding of abnormalities in cardiovascular reflex control in diabetic patients. Spectral analysis and pulse wave analysis are promising approaches to early detection of abnormalities in arterial baroreflex regulatory mechanisms in diabetic patients, but needs further evaluation. Conventional cardiovagal and adrenergic cardiovascular reflex tests remain the investigational cornerstone for detection of autonomic dysfunction and its objective diagnosis.

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