Automated assessment of cardiovascular disease associated with diabetes in rural and remote health care practice

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Abstract

Damage to the autonomic nervous system results in changes in the heart rhythm and rate. Diabetes associated cardiovascular changes related to autonomic nervous system damage may be present anytime prior to manifestation of diabetes. Testing for changes to heart rhythm may provide a means of early identification of cardiovascular disease and allow timely intervention. Identification of cardiac autonomic neuropathy (CAN) in people with diabetes has progressed from simple reflex tests to mathematical analysis associated with heart rate variability. Barriers such as lack of specialists, travel requirements of patients to metropolitan clinics and funding of equipment has restricted the utilisation of cardiovascular screening in diabetes care. We conducted a 3-lead ECG screening trial using 20-minute recordings and analysing the beat-to-beat variation (heart rate variability—HRV) using a computer based analysis, detrended fluctuation analysis (DFA). The method is robust against noise and ectopic beats. 24 traces of controls and 24 of people with diabetes were analysed. The average age of the participants was similar in both the diabetes and control groups. The ratio of females to males was also similar between groups. A significant difference between people with diabetes 1.00 ± 0.22 and controls 1.12 ± 0.18 was observed. There was no significant difference between people with diabetes with and without CAN using DFA. However a trend for people with CAN to have lower mean values (0.91 ± 0.24) than people without CAN (1.05 ± 0.18) or the controls (1.12 ± 0.18) for DFA was found. These advances in ECG interpretation provide an additional option for community health workers in rural and remote areas to assess autonomic neuropathy associated with diabetes before clinical signs are present.

Introduction

Diabetes mellitus is a major health issue facing the Australian community. It is estimated by 2010 that 950, 000 Australians will have diabetes. Complications of diabetes include neuropathy and microvascular and macrovascular changes. These complications can cause foot injuries, renal disease, visual impairment, and cardiovascular disease. Cardiovascular complications in diabetics account for 65% of all diabetic deaths. Cardiovascular disease is caused by both damage to the autonomic nervous system and macrovascular changes. Damage to the autonomic nervous system results in changes in the heart rhythm and rate which causes a decrease in heart rate variability (beat to beat alterations in heart rate). The increased risk of cardiac mortality combined with the rapid progression of autonomic neuropathy makes screening of people with diabetes for autonomic neuropathy vital so that early detection can occur and the appropriate treatment begin.
In rural and remote areas especially, diabetes and cardiovascular disease remains, in many instances, undetected for quite some time.4,7 This lessens the quality of life for individuals and also the outcome of any health care intervention. The recognition of preclinical changes associated with cardiac dysfunction ensures early health care intervention and an overall better prognosis and lifestyle.6–9

**Cardiovascular disease and diabetes**

People with diabetes have an increased risk of CVD, 14.9% of people with diabetes have heart disease compared to 2.5% of the general population. People with diabetes also develop CVD at a younger age. The impact of cardiovascular disease on people with diabetes can be seen by the fact that one of the expected outcomes from the National Diabetes Strategy 1998 was that 80% of all people with diabetes be regularly screened for cardiovascular risk factors with the aim to decrease the incidence of cardiovascular related mortality.1

**Diabetic autonomic neuropathy**

Diabetes commonly causes widespread damage to the autonomic nervous system. The autonomic neuropathy is caused by damage to the small afferent and efferent nerve fibres that innervate visceral organs including the heart. It is estimated that cardiovascular autonomic neuropathy is detected in at least one quarter of Type I and one third of Type II diabetes that show symptomatic diabetic autonomic neuropathy.10 Symptoms of autonomic neuropathy do not occur in all patients although heart rate changes may be abnormal.11 Diabetic autonomic neuropathy increases the risk of ventricular arrhythmias and cardiac mortality when compared with people that have no diabetes or patients with diabetes but no autonomic neuropathy.12,13 In addition a significant deterioration of autonomic neuropathy in people with diabetes subsequent to diagnosis has been observed.14

**Heart rate variability**

Heart rate variability (HRV) refers to the beat to beat alterations in heart rate. Under resting conditions individuals exhibit periodic variations in cardiac cycle time (the distance between each R aspect of a QRS wave measured by an ECG, R-R interval) that fluctuate with the phases of respiration and other physiological and pathological variables (see Figure 1).15

![ECG wave showing R-R interval. Note that the R-R distance varies between consecutive beats](image)

Due to multiple influences on heart rate such as neuronal and endocrine, there is a large HRV in healthy individuals. If one physiological aspect that affects heart rate is damaged then there will be a change in heart rate and a decrease in HRV or a loss of complexity. As the autonomic
nervous system influences heart rate, damage to the autonomic nervous system that occurs in people with diabetes can be measured as a change in heart rate and decrease in HRV complexity.\textsuperscript{16,17}

**Autonomic reflex testing and diabetes**

Reflex testing associated with autonomic nervous system function is able to detect autonomic neuropathy in people with diabetes.\textsuperscript{18,19} Abnormalities in reflex testing was shown to be a good assessment of diabetic autonomic neuropathy and aided in the diagnosis of autonomic neuropathy rather than simply relying on clinical signs. This test battery however, has its limitations. It over simplifies the underlying neural mechanisms and does not account for interaction between the sympathetic and parasympathetic nervous systems.\textsuperscript{17} The reproducibility of the tests is low and there is also difficulty in interpreting the results. Difficulties arise in people who are border line because 13\% of the normal population have abnormalities in one of the tests and the results of the tests worsen with age.\textsuperscript{6,20} The final disadvantage of reflex testing is that it requires the patient to be actively involved in the testing process. Therefore the test takes longer to perform and is more complex, limiting its ability to be used as screening test. Positive results of reflex testing only occur once the autonomic nervous system to the extent where clinical signs and symptoms appear and cardiac function compromised. Therefore it is unable to detect changes at a sub clinical level. These limitations have been addressed by the use of time and frequency domain and non-linear analysis to measure HRV.

**Time and frequency domain analysis**

Time domain analysis is one of the simplest forms of heart rate analysis. It involves recording the R-R interval between successive QRS complexes on an ECG usually taken over 1 minute to 24 hours.\textsuperscript{21} These intervals are then used as data points and analysed with respect to mean and standard deviation. Small differences between people with diabetic neuropathy and controls, when compared with practical autonomic function tests including the Valsalva manoeuvre have been reported.\textsuperscript{22} The increase in sensitivity was in part due to the increased number of data points as the ECG readings were taken over a 24-hour period. Although time domain analysis is more sensitive compared with traditional methods of autonomic neuropathy testing it is not useful as it is based on mean and variance data that may not discriminate between two quite different heart rate records.\textsuperscript{15}

A complex waveform such as HRV is comprised of multiple frequencies. Frequency domain analysis analyses this complex waveform by looking at the different components (frequencies) that comprise the waveform. In HRV the two main frequencies that represent autonomic nervous system activity are the low frequency component (LF; 0.03–0.15Hz) and the high frequency component (HF; 0.18–0.40Hz).\textsuperscript{23} Multiple studies have been performed in people with diabetes using frequency domain analysis of HRV.\textsuperscript{20} Pagani and collaborators compared the results between people with diabetes and a control group. In this study the increase in LF and LF:HF ratio during passive tilt was smaller in people with diabetes when compared to a control group. However, there was no difference between people with diabetes and controls at rest. The study showed that frequency domain analysis could detect changes in the absence of overt clinical signs associated with autonomic neuropathy but only when tilting occurred.

Further research using frequency domain analysis showed a significant decrease in both HF and LF in people with diabetes with autonomic neuropathy compared to a control group when measuring participants at rest, during sit to stand movement, and controlled respiration.\textsuperscript{24} This study, however, did not identify a significant difference between people with diabetes with
autonomic neuropathy and those without autonomic neuropathy in any of the three tests. The study also showed a significantly lower LF:HF ratio in people with diabetes but without autonomic neuropathy when compared with the control group at rest and during tilt, indicating that frequency analysis may have a role in the early detection of autonomic neuropathy. The main problem with frequency domain analysis is its sensitivity to ectopic beats and recording length as well as its limited ability to detect sub clinical changes in heart rate and HRV at rest, therefore limiting its use as a screening test. Furthermore frequency domain analysis is not sensitive to the very low frequency components of HRV that carry important information with respect to complex (non-linear) physiological influences on HR. However, alternate non-linear methods may be able to deal with ectopic beats and the wide range of frequencies that occur in the HRV waveform.

Non-linear analysis

Short-term HRV recordings also contain an irregular (aperiodic) component in addition to the regular (periodic) LF and HF components discussed earlier. This irregular component may constitute up to 70% of the total variance of HRV and is unpredictable or erratic and therefore lends itself better to non-linear analysis. As non-linear analysis of HRV allows the analysis of multiple frequencies it can give information about how the cardiovascular system reacts to other variables that modulate heart rate such as respiration and limbic non-reflex autonomic modulation. It is the interaction of all these different physiological variables that makes heart rate complex. The advantages of non-linear analysis are that smaller differences can be detected when compared with time and frequency domain analysis and it also does not require a stationary signal as ectopic beats do not effect the analysis and a change in HRV is more likely to be identified. Using non-linear analysis, 96 diabetics, 51 with autonomic neuropathy and 45 without were compared with 60 controls of similar age. The results showed a significant difference between all three groups. Therefore non-linear analysis could be used as an independent marker for the early detection of cardiac autonomic dysfunction in diabetics. Further research is required into the reliability of non-linear analysis and it use in screening testing for autonomic neuropathy.

Methods

All individuals were assessed for the presence of symptomatic cardiac autonomic neuropathy using the lying-to-standing index based on R-R intervals obtained from the ECG recorded. Twenty-four traces of controls and 24 of people with diabetes (18 type II and 6 type I) were analysed using a 3-lead ECG recorder purpose written software in our laboratory (SoftECG). The average age of the participants was similar in both the diabetes and control groups 59.9 (25–75) and 58.8 (36–82) respectively. The ratio of females to males was also similar between groups with there being 14 females and 10 males in the diabetes group and 15 females and 9 males in the control group. Student t-tests were used to compare groups.

Results

There was a significant difference between people with diabetes 1.00 ± 0.22 and controls 1.12 ± 0.18 for the DFA. There was no significant difference between people with diabetes with and without CAN using DFA. However a trend for people with CAN to have lower mean values (0.91 ± 0.24) than people without CAN (1.05 ± 0.18) or the controls (1.12 ± 0.18) for DFA was found.
Conclusion

Autonomic neuropathy is a major complication of diabetes. It has been shown to double the risk of cardiac mortality. Testing for autonomic neuropathy in people with diabetes has progressed from simple ECG to HRV analysis using time and frequency analysis of R-R intervals to non-linear analysis of HRV. The use of frequency and non-linear analysis allows autonomic dysfunction to be detected earlier because it can detect changes before clinical signs are present, therefore allowing earlier intervention. This ability to screen patients for autonomic dysfunction will aid in the treatment of complications of diabetes, planning long term treatment strategies and monitoring of patient outcomes. Early detection is also vital in the prevention of the advanced symptomatic stage. However, diagnosing autonomic neuropathy is complex, with multiple methods currently being used to measure HRV. Advances in ECG interpretation that we are investigating provide an additional option for community health workers in rural and remote areas to assess autonomic neuropathy associated with diabetes before clinical signs are present.

References


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