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Clinical screening of diabetes mellitus and coronary heart disease

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Abstract
A non-invasive, clinical system for low-cost screening of diabetes mellitus (DM) and coronary heart disease (CHD) is introduced and tested on patients with known conditions. Specifically, the heart rate variability (HRV) signal is extracted from 30 minutes of electrocardiogram (ECG), during which the patient was requested to perform specific actions. The HRV signal is then used as a diagnostic indicator of the presence of DM and CHD.

Keywords *- HRV, ECG, DM, CHD, Classification*

Introduction

In the United Arab Emirates (UAE) 19% of the people over 20 years of age have Type II diabetes mellitus (DM).[1] Furthermore, 50% of all patients treated in hospitals of the UAE were unaware they were diabetic.[2] Experts estimate 50% of the UAE population will be diabetic within the next 25 years.[3]

Complications due to DM include blindness, kidney failure and disability when amputation is necessary. In addition, in the USA, CHD accounts for 65% of diabetic patient mortality due to heart attack.[4] CHD and cardiovascular disease (CVD) include various dysfunctions of the circulatory system, and accounts, by far, for the greatest cause of morbidity in DM patient. In the UAE, CHD mortality accounted for 25% of all deaths in the year 2000, and 49% of all non-communicable diseases.[1]

Early detection of DM and CHD prior to clinical events, coupled with implementation of preventive management strategies, can delay the progression of these diseases. In fact, proper diet, physical exercise, cessation of smoking, control of blood pressure and reduced cholesterol lowers a patient's odds of myocardial infarction by 19 times.[5, 6]

Success of a screening procedure in clinical practice depends on many factors that often differ from accepted research tests. The clinical procedure must incorporate simplicity, which may be carried out by one person and requires minimal patient cooperation. The procedure must also be safe and entail no unnecessary risk to the patient. Lastly, the procedure must be cost effective, reproducible, time efficient, and have easily interpretable results.

In recent years, the development of cost-effective computers and data acquisition systems to measure non-invasive physiological signals for clinical diagnosis and screening has increased greatly.[7] Non-invasive measurements minimize risk of infection, require no analgesics, and reduce measurement artefact due to patient stress, such as adrenalin and hypertension.

Specifically, much study has focused on changes in the heart rate (HR), which is controlled by the sympathetic and parasympathetic branches of the autonomic nervous system (ANS). The parasympathetic nerves (Vagus) slow the HR and sympathetic nerves accelerate the HR. The variability of the HR (HRV) is the result of a balance between the sympathetic and parasympathetic nerves. These two branches of the ANS serve as a control system for the HR in order to respond to changing conditions of the cardiac load.[8]

The diagram in Fig. 1 describes the basic HR control system that is managed by the ANS and baroreceptors, which are sensors that detect pressure in the aortic arch and carotid arteries. These sensors serve as one means of feedback for the HR control system. Additionally, chemoreceptors are sensors used to measure chemical compounds, such as the pH in the medulla, which in turn, also provide control of the respiration and HR through the release of adrenal medulla.

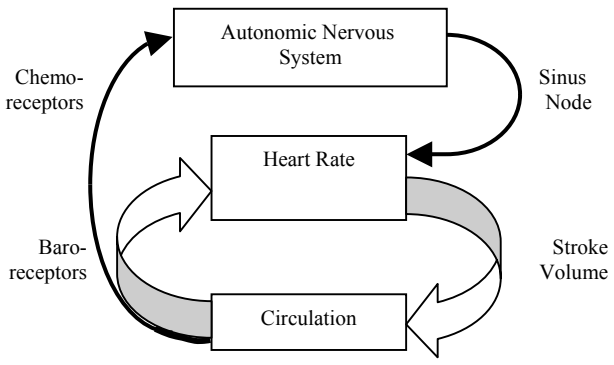

Figure. 1: Basic circulatory system emphasizing HR control.

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Fluctuations in HR are quasi-periodical with changes in morphology, amplitude and phase from one beat to the next. In steady state conditions, these oscillations are maintained around a certain mean value. For the human, with no ANS control, the heart beat is approximately 100 beats per minute (BPM). With ANS control and resting, the parasympathetic response dominates and the HR lowers to approximately 70BPM. During exercise, the sympathetic response dominates and the HR increases accordingly.

The HR may be easily monitored non-invasive in a clinical setting through the acquisition of the ECG. Since the HR is controlled by the ANS, measurement of the HR provides information about the sympathetic and parasympathetic cardiovascular control mechanisms.[9] Additionally, the HRV has been shown to be influenced by respiration, mental stress, CHD, drugs, ectopic beats and age.

Thus, HRV may be used as a means for clinical screening of dysfunction in the circulatory HR control mechanisms. Specifically, reduced HRV may indicate the presence of diabetic autonomic neuropathy (DAN), which has been shown to be an early symptom of diabetes.[10] Furthermore, it has been shown that the HRV frequency spectrum is affected by the presence of CHD and CVD.[11,12]

The HRV information is computed from the ECG, which is acquired from the patient using the Einthoven bipolar electrode positions in order to maximize the height of the QRS complex, per the guidelines of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.[13] The ECG is sampled at 500Hz and the R-waves are detected. The beat-to-beat HR is computed as the interval between the R-wave peaks. Ectopic beats, such as pre-ventricular contractions (PVC), are removed and the HR signal is interpolated to 5Hz. Finally, in order to emphasize the variability in the signal, the trend (information less than 0.02Hz) is removed, per the algorithm in Fig. 2.

In order to evoke a response from the ANS on the HRV signal, the patient is initially requested to lie quietly, supine, while the first five minutes of HRV is collected. The patient is then request to stand after which an additional five minutes is collected. Then the patient is

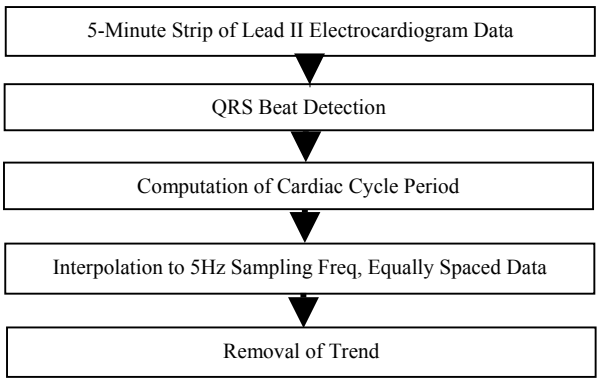

Figure. 2: Algorithm to determine HRV from the ECG.

Table1: Detail level with corresponding frequency range.

Detail Level	Approximate Frequency Range
1	1.30 to 2.50Hz
2	0.63 to 1.30Hz
3	0.31 to 0.63Hz
4	0.16 to 0.31Hz
5	0.08 to 0.16Hz
6	0.04 to 0.08Hz
7	0.02 to 0.04Hz

requested to sit/squat for an additional five minutes. Lastly, the patient is guided to breathe at 9, 12 and 15 breaths per minute, during which, additional five minutes of HRV are collected for each, for a sum total of 30 minutes of HRV information.

Once the HRV has been collected, the signal is characterised by time-frequency analysis using the wavelet transform. Wavelet analysis decomposes a signal into several frequency bands while preserving the event time information, per equation 1. In this case, the events are the particular patient actions. The detail coefficients, $d_j(k)$, describe fluctuations in the signal within each particular band. The approximation coefficients, $a_J(k)$, describe the lowest frequency fluctuations in the signal and include the signal trend. The analysis is efficiently implemented through application of repeated high and low pass filters using scaled and dilated versions of the analysis functions, ψ and ϕ, respectively. This procedure has the benefit of allowing multiple resolutions for each frequency band and time scale.

$$x(n) = \sum_{j=1}^{J}\sum_{k\in Z} d_j(k)\psi_{j,k}(n) + \sum_{k\in Z} a_J(k)\phi_{j,k}(n) \qquad (1)$$

In regards to the HRV signal, wavelet analysis is carried out over a 12th order Daubechies wavelet, as recommend, for best highlighting the variability in the signal.[14] [1] Since the HRV signal is sampled at 5Hz, a 7 level decomposition is carried out in order to obtain the frequency bands of Table I. The wavelet approximation spans the 0 to 0.02Hz frequency band, which is discarded in keeping with removal of the signal trend, per the algorithm in Fig 2.

The wavelet transform is used to decompose the HRV signal of a sample normal patient and displayed in Fig. 3. The detail coefficients are squared in order to display the changes in the relative power of the signal over time.

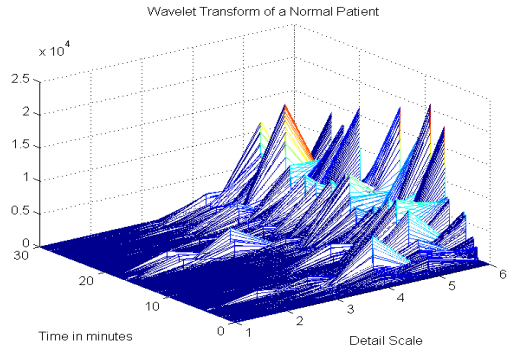

Figure. 3. Wavelet decomposition of a normal patient.

Table2: 5-minute, inter-quartile range of the details.

Detail Level	0–5 (min)	5–10 (min)	10–15 (min)	15–20 (min)	20–25 (min)	25–30 (min)
2	1	2	1	3	2	2
3	16	10	9	11	11	13
4	31	20	14	21	23	20
5	34	61	42	35	61	44
6	17	70	66	93	87	31
7	7	85	142	75	102	23

In order to better prepare the wavelet detail features for classification, the inter-quartile range was determined for each detail level over five minute intervals. This estimates the signal power for each patient action for each frequency band (detail level). The inter-quartile range is the difference between the 75% and 25% percentile, as shown in equation 2, where N is the number of samples, I defines the greatest integer function and S defines a sorting function. The inter-quartile range approximates the signal's variance and gives a robust measure since outlying values are not included in the measure.

$$R = S(x(I(0.75N))) - S(x(I(0.25N))) \quad (2)$$

Therefore, the HRV signal is characterized by 36 values, since the clinical procedure involves six different actions, each of fives minutes, and the 2nd through the 7th wavelet detail coefficients are used. Table II displays the five minute inter-quartile range values for the sample normal patient displayed in Fig. 3.

These analysis features are used as a basis for classification, per the diagram in Fig. 4. The classifier employs supervised learning in order to train it on patients with known DM and CHD conditions.

Specifically, a neural network classifier is trained by using the HRV wavelet feature as inputs and the known patient conditions as output. The commercial package, NeuroShell2 (Ward Systems Group, Inc., Frederick, MD, USA) is used to built a 36 input, 3-layer, 20 neuron hidden layer, and two output neural network. The two outputs indicate the presence of DM (0/1) and CHD (0/1) in the screened patient.

Materials and Methods

The HRV signal was acquired from patients with known DM and CHD conditions. In order to determine the feasibility this clinical screening methodology, a pilot study of 17 patients was done. Also, in order to limit the scope of the effects on the HRV signal, the patients were

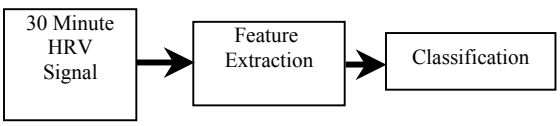

Figure. 4: Characterization and classification of HRV for patient diagnosis and screening.

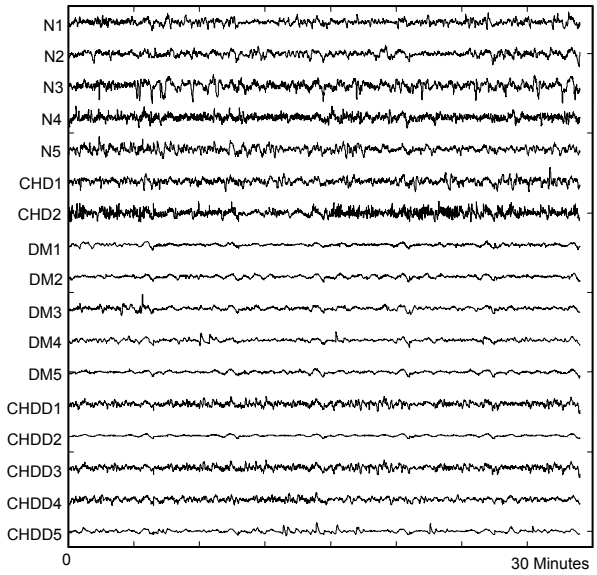

Figure. 5: HRV signal of 17 patients with known conditions.

limited to men between the ages of 45 and 55 years. In addition, it was ensured that none the patients displayed excessive ectopic beats during ECG acquisition. Fig. 5 displays the 30-minute HRV signal for patients with normal (N), DM, CHD, and diabetic CHD (CHDD) labels, according to the patient condition. From the figure, it is readily apparent that the diabetic patients display far less variability than the non-diabetic patients. That is, the non-diabetic patients display a greater range of changes in the HR than the diabetic patients.

Results

The trained classifier was tested using leave-one-out analysis. Specifically, the classifier was trained using all the patients, except one. The classifier was then applied to the one remaining patient and the classification results were determined. This procedure was then repeated for each of the 17 patients and the sum total classification results were used to determine the sensitivity, specificity, positive predictive value, and negative predictive value. The sensitivity is the probability that a diseased patient is correctly classified as having the disease. The specificity is the probability that a normal patient is correctly classified as not having the disease. The positive predictive value is the probability that a person has the disease given a positive classification result, and the negative predictive value is the probability that a person does not have the disease given a negative classification result.

After completing the leave-one-out analysis, it was found that the neural network classifier scored 100% for the sensitivity, specificity, positive predictive value, and negative predictive value for both DM and CHD screening. In other words, the classifier correctly assigned each patient that was not included in the network training.

In order to further test the neural network classifier, leave-one-class-member-out analysis was performed. For this test, the neural network classifier was trained using all the known

Table 3: Classification results for DM and CHD screening.

Test	Sensitivity	Specificity	Positive Predictive Value	Negative Predicative Value
DM	100%	100%	100%	100%
CHD	97%	97%	96%	91%

patients, except one patient from each of the conditions: N, DM, CHD, and CHDD. The trained classifier was then applied to the four remaining patients and the classification results were determined. This procedure was then repeated several times for different members of patient conditions and the sum total classification results were used to determine the sensitivity, specificity, positive predictive value, and negative predictive value. Using this procedure, it was again found that screening for DM scored 100% for the sensitivity, specificity, positive predictive value, and negative predictive. However, the classifier was not able to correctly assign all the patients in screening of CHD, as displayed in Table 3

Conclusion

The results of this new methodology for screening DM and CHD in patients are quite encouraging. However, further investigation is required to statistically prove the benefits of this new clinical screening for DM and CHD over traditional blood-fasting and exercise ECG tests. Although the diagnosis of CHD was found to be not as precise as that for the DM, this procedure provides a new clinical tool for quickly determining a patient's condition, without the requirements of expensive laboratory tests, complex patient procedures, or invasive measurements.

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