Low-cost Detection of Cardiovascular Disease on Chronic Kidney Disease and Dialysis Patients Based on Hybrid Heterogeneous ECG Features Including T-wave Alternans and Heart Rate Variability

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Abstract

Accumulating evidence shows that cardiovascular disease (CVD) contributes substantial burden to dialysis patients, accounting for almost 50 percent of mortality in dialysis population. Traditional clinical risk factors may not totally explain and predict CVD high mortality. The aim of this research is to develop a non-invasive, low-cost method for dialysis patients to evaluate their risks on cardiovascular disease (CVD) by hybrid heterogeneous ECG features including T-wave alternans and heart rate variability. A decision-based neural network (DBNN) structure is used for feature fusion and it provides overall 71.07% accuracy for CVD identification.

1. Introduction

According to the data from Taiwan Society of Nephrology, there were more than 1,100,000 chronic kidney disease (CKD) patients in Taiwan and the number increase day after day. In addition to the data from United States Renal Data System (USRDS), it also revealed that Taiwan had the highest incidence of end stage renal disease worldwide.

Accumulating evidence shows that cardiovascular disease (CVD) in end-stage renal disease contributes substantial burden to dialysis patients, accounting for almost 50 percent of mortality in both Chinese and Caucasian dialysis population. The death rate for all US dialysis patients in 1998–2000 was 236/1000 patient-years [1]. Of importance was the observation that cardiovascular disease mortality rate in end-stage renal disease patients are 17 times higher than the general population. The number is unacceptable high. Unfortunately, the reason for high mortality is still uncertain. The management of CVD in renal patients is a challenge for clinicians.

In the USRDS database, the single largest specific cause of death is attributed to arrhythmic mechanisms or sudden cardiac arrest (SCA) [5]. The 29.7 percent of deaths in prevalent dialysis patients are related to SCD [1]. Some studies also found similar findings on the relative contribution (22 to 26 percent) of sudden death to all-cause mortality in dialysis patients [2, 6].

Some previous researches verified that HRV indicates the risk of sudden cardiac death (SCD) events. Ichimaru et al. found that the respiratory peak of the heart rate variability (HRV) in SCD patient was disappeared during the night time one-week before death [7]. A research observed two HRV measurements, standard deviation of mean of sinus R-R intervals (SDANN) and mean of SD (SD), from 24 hrs HRV. The evidences show that HRV is low in patients who experience SCD, and is high in young healthy subjects [8].

In addition, repolarization alternans phenomena provides a safe, noninvasive maker for the risk of SCD, and has proven equally effective to an invasive and more expensive procedure - invasive electrophysiological study (EPS), which is commonly used by cardiac electrophysiologists. T-wave alternans (TWA) refers to beat to beat variability in the timing or shape of T waves on the surface electrocardiogram (ECG). The United States Food and Drug Admistration (FDA) has approved TWA for noninvasively predicting the risk for life – threatening ventricular arrthymias, and has recently been approved for reimbursement by the Centers for Medicare and Medicaid Services (CMS). Now TWA had been one of the most commonly evaluated as a tool in risk stratification for SCD.

Artificial neural networks (ANNs), linked to artificial intelligence (AI), are mathematic models which inspired by biological neurons which construct the human brain. In the past few years, a number of researches using ANN models for cardiovascular risk assessment and predication have been proposed to the medical community. Especially, Grossi [3] indicated that the use of fuzzy logic

and ANN approaches seems to better address both the challenge of the increasing complexity/nonlinear of predisposing factors linked to the occurrence of cardiovascular events data and the prediction of future events on an individual level. The ANN models are able to assist physicians in defining and quantifying the risk level of an individual patient with regard to developing major cardiovascular events in the following years. For example, Viazzi et al. [4] evaluated how well an artificial neural network (ANN) can assess cardiovascular risk profile on the basis of estimated creatinine clearance and routine, low-cost clinical data. They found the ANN model can accurately identify the patient's risk status by comparing with thorough clinical work-up. However, instead of observing cardiovascular risk on patients with essential hypertension, this research only focused on cardiovascular risk assessment and prediction of ESRD patients by using multiple ANNs.

The aim of this research is to develop a non-invasive, low-cost method for dialysis patients to evaluate and to monitor their risks on cardiovascular disease (CVD). The hybrid heterogeneous ECG features, including T-wave alternans and HRV, are fused by ANN to find out the risk factors of CVD. We also demonstrate the HRV and TWA difference between chronic hemodialysis patients with and without CVD.

2.   Methodology

Fifty CKD hemodialysis patients were recruited and monitored over three years under IRB regulation at Tzu-Chi General hospital, Taiwan. Cardiologists categorized the population into two groups: 27 and 23 patients with and without CVD, respectively. Their ECG signals have been recorded for 5 minutes at supine for every 6 months for HRV and TWA analysis. The ECG was sampled at 500Hz by using the Biopac MP35 system which is an integrated solution for the measurement of physiological signals. The MP35 (Bipoac Systems, Goleta, CA, USA) with the Biopac Student Lab PRO software was used for data acquisition.

2.1.   Processing on heart rate variability and T-wave alternans

In order to obtain HRV features, digital filtering technologies are applied to remove possible interferences. Pan and Tompkins method was used in this research to determine all the R points in order to calculate R-R intervals [11]. After QRS complexes detected, time-domain and frequency-domain analysis are applied. In time domain, HRV measures the beat-to-beat (RR) intervals. The time domain features include the mean and standard deviation (SDNN) of the RR intervals. There are also other commonly used parameters such as coefficient of variation (CV), root mean square of standard deviation (RMSSD), standard deviation of standard deviation (SDSD), NN50, pN50, where the NN50 is the number of consecutive RR intervals differing more than 50ms, and the pNN50 is the percentage value of NN50 intervals.

In the frequency-domain analysis, features are obtained from the power spectrum of the RR series. In this research, RR tachogram described as the two-minute (short-term) continuous series of RR intervals and was re-sampled at 4 Hz with linear interpolation. After that, a fast Fourier transform (FFT) and Welch method were used.

TWA was computed spectrally from the ECG during ventricular pacing, and TWA phase reversal was reflected by a discontinuity in T-wave oscillation after single ventricular extrasystoles. Briefly saying, the spectral method (SM) averages power spectra of 128 time-aligned T-wave with the beat-to-beat amplitude fluctuation on each sampling point of T-wave. The averaged spectrum (PSD_{SM}), the traditional SM spectrum, appears as the spectral peak at the frequency of 0.5 cycles per beat (cpb). Hence, the alternans ratio (AR) can be obtained by:

$$AR = \frac{P_{0.5} - noise}{\sigma_{noise}} \qquad \ldots(1)$$

where $P_{0.5}$ is the amplitude of peak at the frequency 0.5 cpb; *noise* and σ_{noise} are average and standard deviation of the noise registered in the spectrum outside the alternans frequency, 0.5 cpb. In our research, the noise band is at range [0.42 0.46] cpb, and $P_{0.5}$ is the maximum value at range [0.47 0.5] cpb by considering potentially TWA frequency shifting. In addition, average alternans voltage, which is microvolt alternans on T-wave amplitude, is calculated.

2.2.   Decision-based   neural   network (DBNN):

A decision-based neural network (DBNN) is a member of the ANN supervised learning family, which uses both reinforced and antireinforced learning rules. That is, the system adjusts the weight vector either in the direction of the gradient of the discriminant function or in the opposite direction. The DBNN not only adopts nonlinear discriminant functions but also uses a hierarchical structure to accommodate a versatile nonlinearity [12]. The structure of a simple DBNN is given in Figures 1.

M neurons correspond to M different classes that are to be identified. M is equal to 2 in this study to distinct CVD or non-CVD group. The system input is a feature vector $\mathbf{x} = (x_1, x_2, x_3,...,x_N)$ that represents N ECG features which are fed into M different classes. Each neuron i implements a discriminant function $\phi(\mathbf{x}, \mathbf{w}_i)$, where $\mathbf{x}$ and $\mathbf{w}_i$ are the input and weight vectors, respectively,

for the neuron i. The outputs of these neurons are fed to a MAXNET which determines the winner and the class corresponding to the winning neuron.
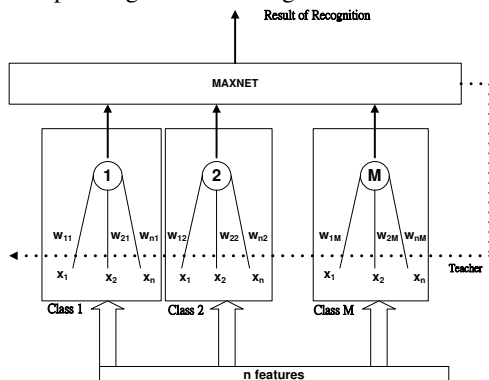

Figure 1. A simple DBNN structure to classify persons into M groups, where $\mathbf{x}$ and $\mathbf{w}_i$ are the input and weight vectors. The weight vectors are adjusted by the feedback during the training process.

The algorithm of the decision-based learning rule is as follows: Suppose that $S = \{\mathbf{x}^{(1)},...,\mathbf{x}^{(L)}\}$ is a set of given training input vectors, where L is the number of training vectors. Each of the training vectors corresponds to one of the M classes $\{\Omega_i, i = 1,...,M\}$. The output of each class is modeled as a subnet with discriminant functions $\phi(\mathbf{x}, \mathbf{w}_i)$, $i = 1,...,M$. Suppose that the l th $(1 \le l \le L)$ training vector $\mathbf{x}^{(l)}$ is known to belong to class Ω_i and the subnet outputs $\phi(\mathbf{x}^{(l)}, \mathbf{w}_j) > \phi(\mathbf{x}^{(l)}, \mathbf{w}_m)$, $\forall j \ne m$, where the winning class is the j th class, an arbitrary class is the m th class, and the correct class is the i th class.

If $j = i$, then the feature vector $\mathbf{x}^{(l)}$ is correctly classed and nothing needs to be updated.

If $j \ne i$, it means $\mathbf{x}^{(l)}$ is misclassified. Hence, the weight taps need to be updated in order to get the correct classification, and then the following update is performed.

Reinforced learning is applied to neuron i (which should have the larger output):

$$\mathbf{w}_i^{(l+1)} = \mathbf{w}_i^{(l)} + \Delta\mathbf{w} \qquad \ldots (2)$$

Antireinforced learning is applied to neuron j (whose output should not be larger than the output of neuron i):

$$\mathbf{w}_j^{(l+1)} = \mathbf{w}_j^{(l)} - \Delta\mathbf{w} \qquad \ldots (3)$$

Other neuron weights remain unchanged.

$$\mathbf{w}_k^{(l+1)} = \mathbf{w}_k^{(l)}, \qquad \forall k \ne i, j \qquad \ldots (4)$$

where $\Delta\mathbf{w} = \eta\nabla\phi(\mathbf{x}^{(l)}, \mathbf{w})$ is the step size for the weight changes. $\nabla\phi(\mathbf{x}^{(l)}, \mathbf{w})$ is the gradient of the discriminant function and η is a convergence constant which

represents a positive learning rate. For more details, the gradient vector of the function ϕ with respect to $\mathbf{w}$ is denoted as

$$\nabla\phi(\mathbf{x}, \mathbf{w}) = \frac{\partial\phi(\mathbf{x}, \mathbf{w})}{\partial\mathbf{w}} = \left[\frac{\partial\phi}{\partial\mathbf{w}_1}, \frac{\partial\phi}{\partial\mathbf{w}_2}, ..., \frac{\partial\phi}{\partial\mathbf{w}_M}\right]^T \ldots (5)$$

where M is the total number of parameterrs. ϕ is set as radial basis function in this investigation.

3.   Results

There are total of 26 heterogeneous ECG features which are evaluated by the statistical t-test and the DBNN soft fusion sensor, including HRV time-frequency features, and T-wave alternans ratio and cumulative alternans voltage.

3.1.   Statistical results

All time domain HRV features shows no significant on independent samples test and subjects are grouped by CVD status. The entire statistical significant features are listed in Table 1 and 2 with mean, standard deviation, and p values. Patients induced into CVD (n=23) had greater TWA magnitude (V_{alt}: 0.24±0.24 $\mu\nu$ vs 0.09±0.06 $\mu\nu$; P=.008) and cumulative alternans voltage (CAV: 24.21±24.41 $\mu\nu$ vs. 9.04±6.46 $\mu\nu$; P=.008) than those who has no CVD (n=27). The chi-square test showed significance between TWA and CVD (Alternans ratio>2.5, P=.028). Dialysis patient with CVD is significant older then the patient without CVD. The LF and LF/HF are significant smaller in CVD group but the HF is less in non-CVD group.

Table 1. HRV measures in patients grouped by CVD status

	without CVD(N=27)	with CVD (N=23)	p value
LF (nu)	57.96±26.14	43.00±20.64	0.031*
HF (nu)	42.04±26.14	56.99±20.64	0.031*
LF/HF	2.81±2.71	1.11±1.21	0.006*
Age (yr.)	55.60±13.99	69.98±11.80	0.000*

Data represent mean±SD

Table 2. TWA measures in patients grouped by CVD status

	without CVD(N=27)	with CVD (N=23)	p value
CAV	9.04±6.46	24.21±24.41	0.008*
Valt	0.09±0.06	0.24±0.24	0.008*

Data represent mean±SD

In statistics, the R-squared value is the fraction of the variance in the data that is explained by a regression. It is defined as the ratio of the sum of squares explained by a regression model and the total sum of squares around the

mean. It can be referred to as the proportion of variation explained by the model. Table 3 shows that our ECG essential features explain 32.1% of the variability of CVD correlation. The results are described in table 3.

Table 3. Correlation coefficient table formed by calculating the relationship between features and CVD.

Correlations

	CAV	FCA V	Valt	FValt	LFnu	HFnu	LF/H F
Pearson Correlati on	.409	.342	.409	.342	-.305	.305	-.371
Sig.(1-tailed)	.002	.008	.002	.008	.016	.016	.004

N=50,R^2=32.1%

3.2   DBNN classification results

The above statistic analysis was followed to observe potential predictors, and then the decision-based neural network (DBNN) is used to fuse heterogeneous features. Parameters of DBNN are set as epoch for 15000 times, step size for 0.01. The algorithm runs 30 times which are averaged as accuracy results. The DBNN structure is N-2-1 which N is the number of features with radial basis kernel. The DBNN model with selected features provides overall 71.07% accuracy. The ROC curve (AUC=0.66023 and S.E.=0.07818) is plotted in figure 2.
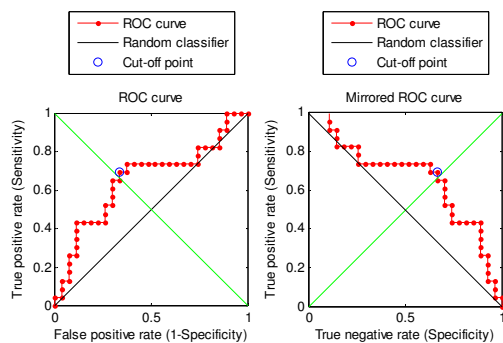

Figure 2. The ROC curve presents the performance of DBNN soft fusion sensor.

4.   Conclusions and discussions

Hybrid TWA and HRV successfully provide risk indicators and classification for CKD patients with or without CVD. According to the statistical results, dialysis patients with CVD are older and have a cardiac autonomic dysfunction as manifest by decreased HRV. Future work may involve more data samples, trace the subject in the longitudinal scale, and use probability to provide the degree of CVD risk, but binary numbers.

Overall, our system potentially provide physicians a low-cost, non-invasive method to screen CKD patients in advance for CVD prevention, sudden cardiac death (SCD) reduction, and future insurance cost subtraction.

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