Effect of hemodialysis on autonomic dysfunction in patients with chronic renal failure

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ABSTRACT

Objective: The main objective of this study is to use the method of complex demodulation combined with posture entrainment protocol (changing from supine to standing position) to characterize the autonomic dysfunction before and after hemodialysis session in patients with chronic renal failure.

Methods: Twenty patients maintained on hemodialysis for an average 18 months were studied. All patients were dialysed regularly three times a week, each time for 4 hours. Electroencephalograms were measured for ureamic patients before and after hemodialysis. Heart rate variability signals derived from electroencephalograms were recorded during the supine and standing positions. Complex modulation method is employed to investigate the sympathetic and parasympathetic activity before and after hemodialysis.

Results: It is possible by using experimental posture entrainment protocol (supine and standing positions) combined with the method of complex demodulation to produce the average low and high frequency response of heart rate variability mediated by autonomic nervous system for twenty uraemic patients before and after hemodialysis sessions in both supine and standing position. The high amplitude of low and high frequency response of heart rate variability of twenty uraemic patients on standing and poststanding after hemodialysis sessions indicates the improvement of autonomic function compared with the same patients before hemodialysis sessions ($p < 0.001$). The decrease of level of chemical components in blood such as creatinine and urea after hemodialysis increases the modulation of stimulus (posture entrainment) and consequently the better function of autonomic nervous system.

Conclusion: The analysis of heart rate variability signals for twenty uraemic patients before and after hemodialysis using complex demodulation combined with posture entrainment protocol seems promising in assessing the autonomic function in chronic renal failure patients. Further studies may be needed to develop quantitative indices for possible screening and early diagnosis of autonomic dysfunction in end stage renal failure using this methodology.

Keywords: Hemodialysis, complex demodulation method, entrainment, autonomic nervous system.

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Patients with chronic renal failure often have reduced nerve conduction velocities.[1,2] They may also have dysfunction of autonomic nervous system.[3]The etiology of these findings is unknown but there are several studies on the development of peripheral neuropathy and on the effect of treatment on the nervous system.[4] There is some evidence that at end stage renal failure, autonomic dysfunction is more severe in pre dialysis patients than those on dialysis.[5] Lang and Forsstrom[6] showed that the nerve conduction velocities improved after single haemodialysis (HD) session. Most previous studies

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used to assess the autonomic function based on either measures of R-R interval variation or power spectra of heart rate variability (HRV) signal using fast fourier transform method (FFT)or auto-regressive methods.[7-9] Ewing et al[7] have compared different tests for autonomic neuropathy based on medical index defined as (HR Max - HR Min) during deep breathing. Powerantz et al and Pagani et al[8,9] used the power spectrum of HRV signal to test and assess the autonomic function for normal subjects and diabetic patients. Actually, the use of FFT method or auto-regressive methods have numbers of constraints specially in quantifying heart variations. These constraints can be summerized as follows: 1. It provides a time averaged power peak, assuming stationarity of data which did not exist exactly in heart rate data. 2. According to Fourier and auto-regressive analysis about its peak (which is the case of HRV signal), the power peak at the fundamental frequency will be smaller than for a signal that is symmetric about its peak. Therefore, spectral analysis is most useful in the assessment of sinusoidal variations (regular variations). The HRV vary in irregular and asymmetric way which may conclude that spectral analysis based on Fourier or auto-regressive methods is not appropriate to assess the heart rate variability signal properly. The application of complex demodulation method (CDM) has been used to assess autonomic function in healthy subjects and diabetic patients.[10-12] Shin et al[10] used CDM to examine the effect of autonomic nervous system (sympathetic and parasympathetic) on heart rate where data were analyzed from dogs under specified protocol. Hayano et al[11] applied CDM to young healthy subjects to determine the time-independent responses of low and high frequencies of heart and blood pressure variability signals during posture tilt. Also, Kamal[12] used CDM combined with posture entrainment protocol to assess the autonomic function for both normal subjects and diabetic patient suffering from neuropathy.

Methods. Twenty patients (12 males, 8 females, age 53 ± 5.5 years, range 37-69 years) on haemodialysis for an average of 18 ± 0.8 months (range 8-36 months) accepted to participate in this study. All patients were stabilized on maintenance hemodialysis before this study. The patients were dialysed with Gambro AK-10 system using hollow fibre (Nephross 1m2, Organon Teknika, Turnhout, Belgium) dialysers. The acetate-buffered single pass dialysate flow was 500 ml/min and blood flow 150-200 ml/min. All patients were dialysed regularly three times a week, each time for 4 hours. More dtails about hemodialysis procedure were given by Zucchelli et al.[4]

Experimental Procedure. Electroencephalograms were measured for uraemic patients before and after HD in supine and standing position. Positive standing (SS+) means that patients have 3 baseline recording of ECGs followed by a period of 30 s (pre SS+) as shown in Figure 1. Both baseline and Pre SS+ period Recording was done in supine position. By the end of pre SS+ period (30s), a tone was voiced indication standing for 30s period, followed by 30 s period after standing (post standing SS+). Negative standing (SS-) means that patients have a 3

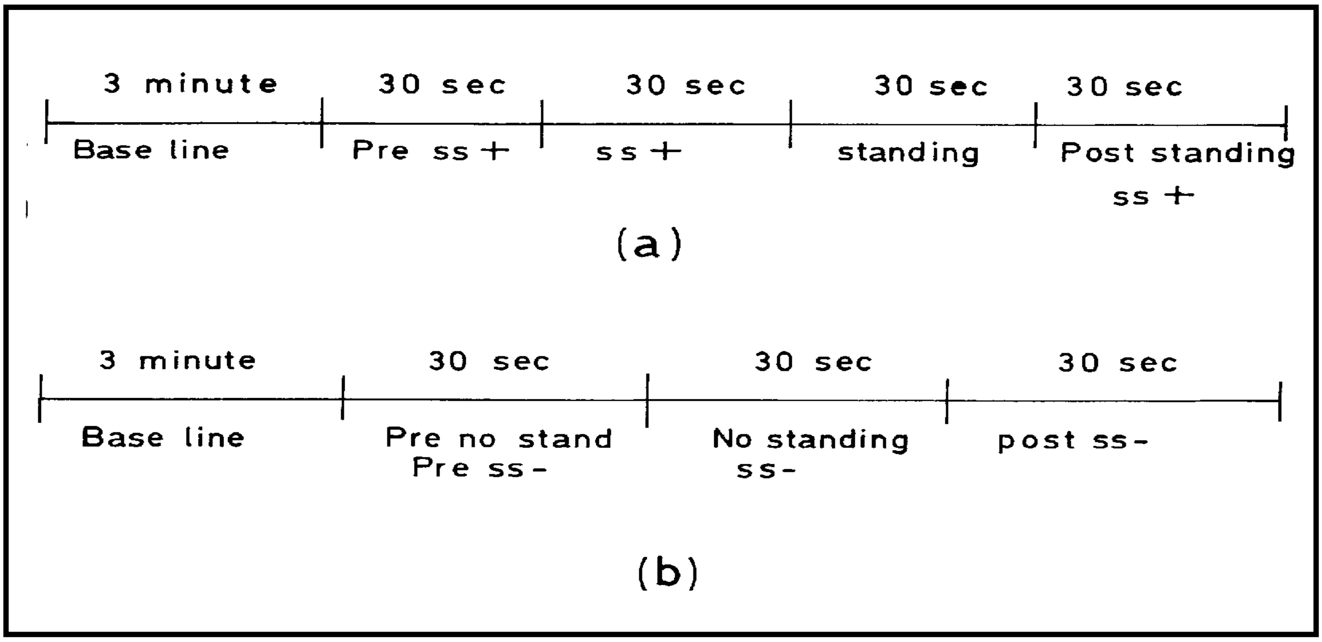

Figure 1 - Experimental protocol. a) Standing condition b) Supine condition.

min base line recording of ECGs, followed by a period of 30s,but by the end of this period (30s), another tone was pulsed indicating no standing period of 30s (SS-) followed by another 30 s period called post no standing period(post SS-). This protocol was repeated for every patient before and after HD. Baseline recording of ECGs was done in supine position to monitor and check ECGs patient and adapt the patient to the environments parameters such as temperature etc. Each patient had two study periods in two positions ie supine and standing position before HD and 15 min after HD. The experimental procedure is shown in Figure 1. During the supine and standing positions periods, ECGs were recorded from bipolar chest lead om magnetic tape by four channel FM-tape recorder (Epsylon Labcorder MR-899, T-251, Epsylon Industries Ltd, North Feltham, Middlesex, UK). Figure 2 illustrates the derivation of HRV signals fron ECG. The technique used in this study to produce HRV signals is based on the hardware circuits described by Cohen et al[13] to detect R-R interval and produce HRV signals. The HRV signals were then passed through two 12 bit A/D converters at 10 Hz sampling rate and the interfaced to Pentium PC with 350 MHz and RAM of 16 Mbytes. The A/D converters were designed so that the first conversion would occur when the first R wave of ECG was detected.The stored HRV signals of twenty uraemic patients before and after HD were then transferred to CDM computer package stored on PC to produce the low and high frequency response of HRV signal in supine and standing position. A rank sum test, a non-parametric analog of independent-samples t-test, was applied to The data of both groups and results indicate that patients before and after HD are significantly different at 0.001 level(p> 0.001).

Complex Demodulation Method. Complex demodulation method (CDM) is a recent approach that can be applied to describe features of data that would be missed by harmonic and spectral analysis. It enables us to describe the amplitude and phase of particular frequency components of a time series as a function of time. As indicated in Bloomfield[16], suppose that a set of data contains as a perturbed periodic component (1) $X(t) = R(t) . x(\cos f_0 + \varphi(t))$, Where $\{R(t)\}$ is slowly changing amplitude and $\{\varphi(t)\}$ is a slowly changing phase. The aim of the CDM is to extract $R(t)$ and $\varphi(t)$ if we know the frequency f_0. Now the complex form of (1) may be written Using Euler's equation as (2) $X(t)= R(t) . \mathrm{Exp}(i\{ f0\ t +\varphi(t)\}) + \mathrm{Exp}(-i\{ f0\ t +\varphi(t)\})$ divided by 2. Assuming that $Y(t)= X(t) . 2 \mathrm{Exp}(-if_0t)$, Then (3) $Y(t)= R(t) . [\mathrm{Exp} (i\varphi(t)) +\mathrm{Exp}(-\{ 2f_0t +\varphi(t)\})\}$. The first term of equation (3) is the one we want to extract the sequence $\{R(t)\}$ and $\{\varphi(t)\}$. The second term,which

Table 1 - Mean heart rate, serum creatinine, urea and potassium levels before and after the hemodialysis (mean ± SEM).

	Before HD	After HD	Significant (p)
HR (1/min)	74.2 ± 1.34	87 ± 4.09	0.001
Creatinine (umol/l)	974.9 ± 73.7	500.9 ± 50.9	0.001
Urea (mmol/l)	40.3 ± 4.6	17.4 ± 2.8	0.001
Potassium (mmol/l)	5.72 ± 0.24	3.89 ± 0.16	0.001
N (Total)	20	20	

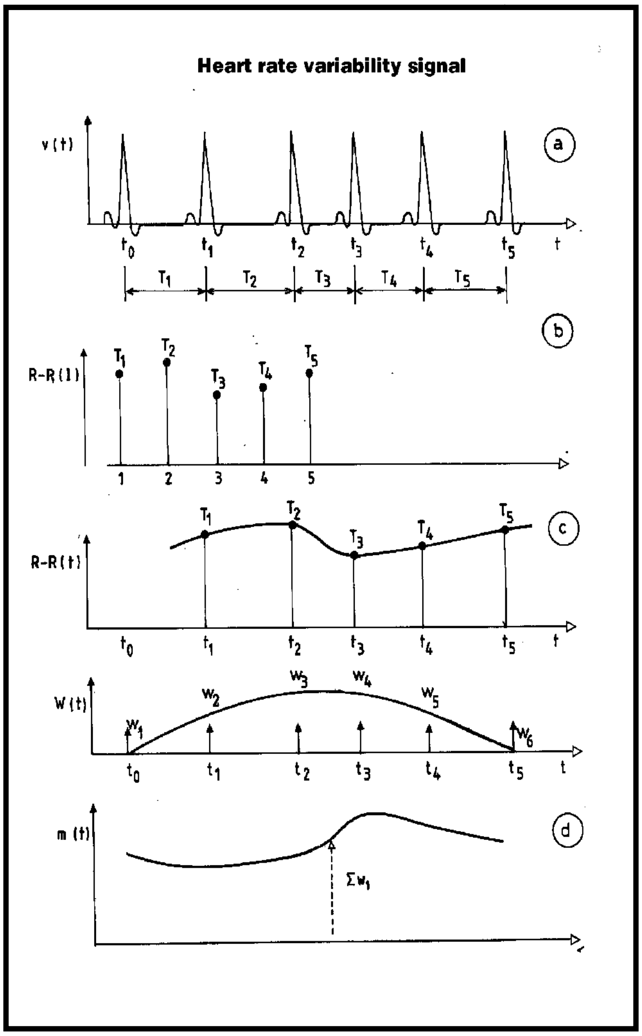

Figure 2 - Derivation of HRV signal from ECG: a) ECG b) Detection of R-R Interval c) Construction of HRV signal d) Smoothed HRV signal using antialiasing.

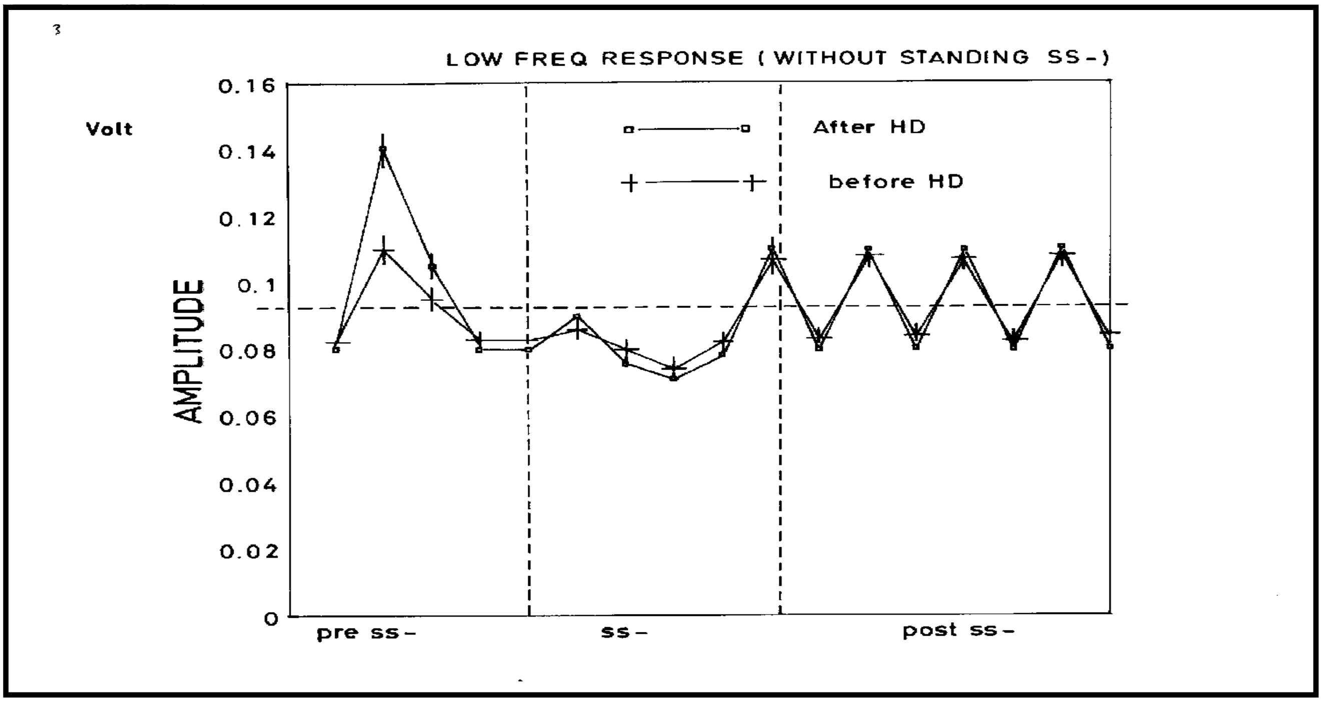

Figure 3 - Low frequency amplitude response of demodulation complex filter for uremic patients before and after HD in supine position. A reference dotted horizontal line at the average of 30s data before pre SS-. Bars indicate standard errors of amplitude in patients before and after HD.

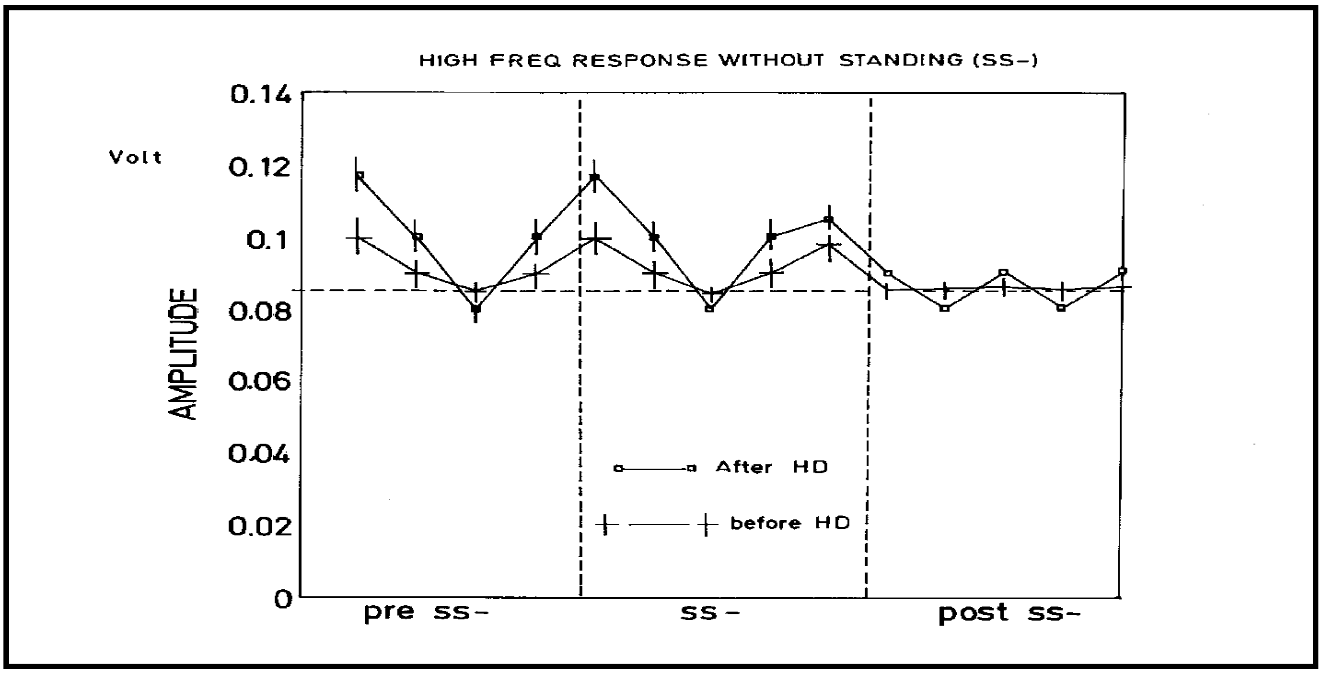

Figure 4 - High frequency amplitude response of demodulation complex filter for uremic patients before and after HD in supine position. A reference dotted horizontal line at the average of 30s data before pre SS-. Bars indicate standard errors of amplitude in patients before and after HD.

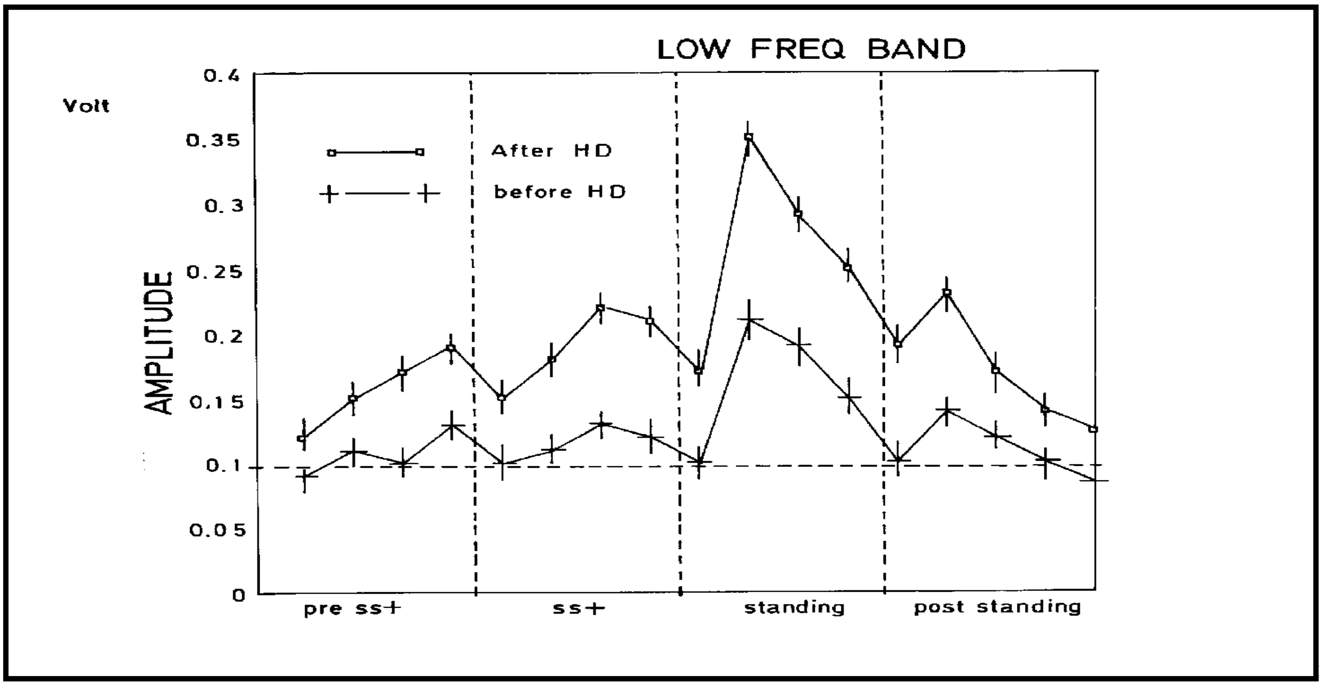

Figure 5 - Low frequency amplitude response of demodulation complex filter for uremic patients before and after HD at standing. A reference dotted horizontal line at the average of 30s data before pre SS-. Bars indicate standard errors of amplitude in patients before and after HD.

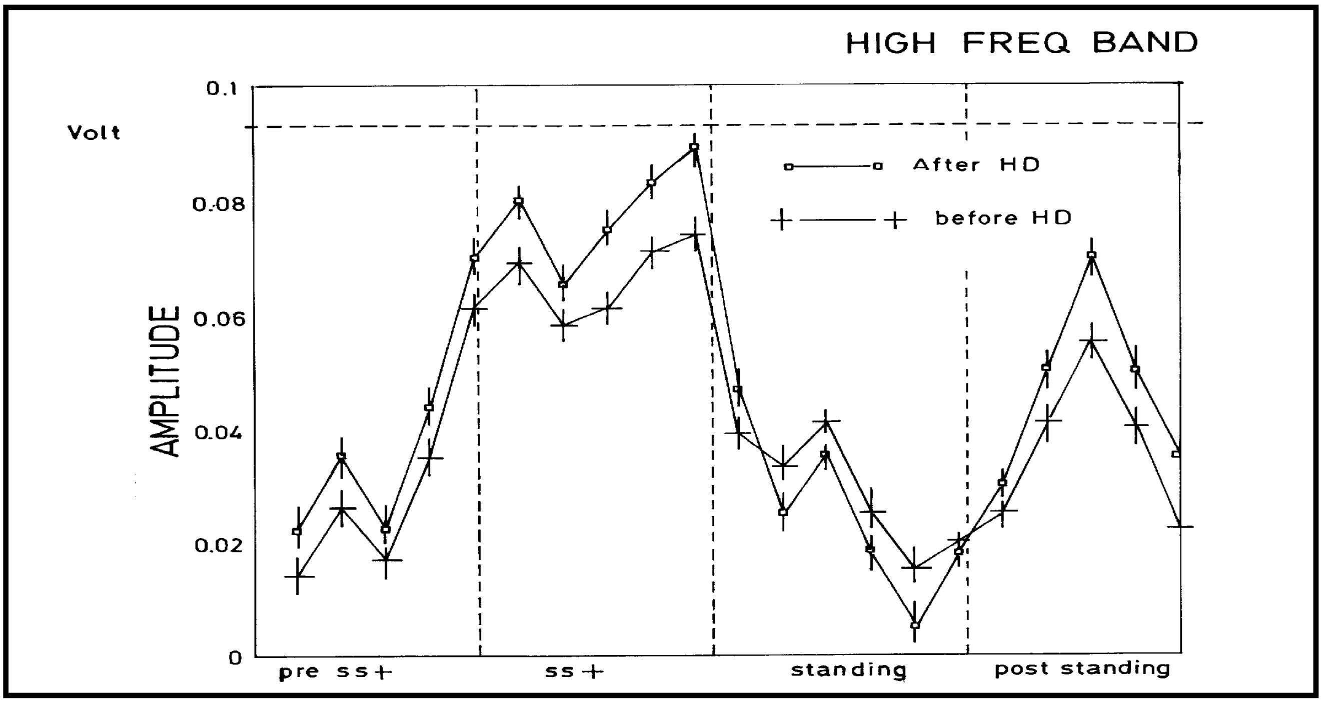

Figure 6 - High frequency amplitude response of demodulation complex filter for uremic patients before and after HD in supine position. A reference dotted horizontal line at the average of 30s data before pre SS-. Bars indicate standard errors of amplitude in patients before and after HD.

is a perturbed complex sinusoid with frequency $-2 f_0$, has to be removed before we can proceed.This can be done using a low pass filter. Let Z(t) be the complex signal when Y(t) is passed through a low pass filter. Then Z(t)= R(t). Exp[iφ(t)}. (4) Therefore R(t) and φ(t) can be recovered as fellows R(t) = (Z\(t)|,φ(t) = tan[imag(x)/real(x)], where x=Z(t)/|Z(t)|.

With respect to frequency domian, it can be implemented by shifting each frequency band of interest to zero frequency and then passing through a low pass filter. With respect to time domain as indicated by equation (1) to (4), the results of complex demodulation show change of signal amplitude and phase around a given frequency f0 over time. This can be applied by a software package prepared by the author to complex demodulate the HRV signal extracted from ECGs and to examine the change in autonomic dysfunction of uraemic patients before and after HD due to change of position from supine to standing across time(posture entrainment). In this study we complex demodulated the sampled HRV data series at 0.3 Hz with low pass filter of corner frequency 0.18 Hz (Butterworth filter type) which covers the range of high band frequency of HRV data series which ranges between 0.17 and 0.4 Hz. With respect to low band frequency, the complex demodulating frequency is 0.0024 Hz with a low pass Filter corner frequency of 0.15 Hz which covers the range 0-0.15 Hz.

Results. Figures 3-6 show the average amplitudes of uremic patients before and after HD during supine and standng position. The 50 point (5s) average was taken from amplitude results to present SS+ and SS- perids athe high frequency (complex demodulation at 0.3Hz) and low frequency(complex demodulation at 0.0024 Hz).This averaging results in a smother curve without losing statistical properties. Referring to Figures 3-6 ,which are the experimental results in 50 point average form, each curve is compared with a reference dotted line at the average of 30s data before the pre SS interval(the horizontal dotted line). Figures 3 and 4 show 50 point (5s) average of the low and high frequency response amplitude foe uraemic patients before and after HD during standing position with also a reference dotted horizontal line at the average of 30 s data before pre SS+. Table 1 shows the HR, urea, serum creatinine and potassium levels before and after HD. It is clear from Table 1 that there is correlation between changes in creatinine level which is measured using spectrophotometer instrument and heart rate variation. In fact, decreasing creatinine level from 975 (73.7 before HD to 500 (50.2 (umol/l) after HD, led to increase heart rate variation from 74.2 (1.34 before HD to 87 (4.59 (1/min) after HD, despite the increase of heart rate after HD.

Discussion. In this study, we apply methodology based on CDM combined with posture position as stimulus according to specified experimental procedure. This method, CDM has been applied by Kamal[12] to assess the autonomic nervous system for normal groups and diabetic group. Actually, it has the ability to provide amplitude time description of HRV signal necessary to characterize and then assess the autonomic nervous system via monitoring the change in autonomic regulation under supine and standing position.[10-12] Looking to Figure 3, the fluctuations of low frequency amplitude response is not significant in supine position for uraemic patients before and after HD except for the period of pre SS-. On other hand,in Figure 5, the fluctuation of low frequency amplitude response is clear and the increase in amplitude for uraemic patients after HD, in standing period, is evident. The interpretation of this increase in fluctuation may be attributed to the importance of combining posture entrainment (standing stimulus) with CDM to the activation of the sympathetic autonomic control system upon standing.This sympathetic activity is related to the low frequency band (0.0125- 0.04 Hz).[9,14,15] The reason for this activation is perhaps the change in some metabolic factors caused by HD as illustrated in Table 1I[4] or decreasing the mental stress for uraemic patients after HD.[14] Actually,the decrease of the level of serum Creatinine,Urea and Potassium levels with increasing heart rate variation after HD is significant as shown in Table 1. These chemical components may affect the function of autonomic system and inhibit the modulation of posture entrainment. Pagani et al[9] mentioned the dysfunction of autonomic nervous system of patients with depression and mental stress. This may suggest that the ureamic patients after HD become less exposing to mental stress due to lowering the levels of chemical metabolic factors listed in Table 1, which result to increase heart rate variation and better autonomic function. Referring to Figures 4 and 6 for high frequency response, once again Figure 4 indicates lower amplitude response before and after HD without Stimulus(standing). However, Figure 6 shows higher amplitudes specially in post standing period for patients after HD compared to the same patients before HD. This may be attributed to the restraining force of parasympathetic activity which is associated with high frequency band (0.18- 0.4 Hz)[17,18] and delayed the higher amplitude response to post standing period instead of standing response as shown in Figure 6. Again, it is worth noted as shown in Figure 5, the influence of low frequency band for uraemic patients upon standing after HD which may be correlated to vasomotor activity manifesting itself in body control oscillations as the blood pressure oscillation at 0.1

Hz[19] and thermoregulatory oscillation at 0.033Hz which existed in the low frequency band of amplitude response (0.0125-0.04Hz).[9,14,15] Despite, CDM seems to be a valuable tool, its usefulness is limited by its inability to separate the effects of two peaks which are very close together in frequency due to practical limitation of the minimum width of low pass filter. However, this limitation is not major one in our application since the peaks of interest are far enough apart to be separated. It should also be noted that some narrow bandwidth low pass filter will produce ripples in the pass band and cause smearing of the result. Therefore we choose a Butterworth filter for this application because it produces a maximally flat amplitude response approximation in the pass band.[20]

In conclusion, the analysis of HRV signals for uraemic patients before and after HD using the CDM combined with posture entrainment (standing stimulus) seems promising in assessing the autonomic dysfunction in chronic renal failure patients. Further studies may be needed to develop quantitative indices for possible screening and early diagnosis of autonomic function in end stage renal failure using this methodology.

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