Mike Zhu

PROJECT TITLE: Dynamic Novel Cardiac Imaging Parameters in Home Nocturnal Hemodialysis

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SUMMARY:

BACKGROUND: Most patients on dialysis have left ventricular hypertrophy (LVH) as seen on cardiac imaging. Nocturnal home hemodialysis (NHD) may produce regression of LVH and may also improve other cardiac and non-cardiac parameters.

OBJECTIVE: To evaluate whether NHD improves cardiac parameters as assessed by cardiac imaging, and to explore whether this improvement correlates with any of the other measures of health we used.

METHODS: This observational cohort study involved information from cardiac imaging, medical history, clinical examination, lab data, and quality of life data from five patients, collected when they began NHD and again at one-year follow-up.

RESULTS: Left ventricular mass index (LVMI) decreased for all patients at follow-up from $35\pm2 g/m^2$ at baseline to $33\pm2 g/m^2$ at 12 months ($p<0.0009$). Left atrial volume index (LAVI) also decreased for all patients at follow-up, from 140 ± 2 to $136\pm3 mL/m^2$ ($p<0.009$). Diastolic dysfunction improved in almost all patients ($p=0.06$) at follow-up. Pre-dialysis systolic blood pressure decreased from 118 ± 13 to 107 ± 12mmHg ($p<0.02$) at follow-up.

CONCLUSION: NHD improves LVMI, LAVI, and blood pressure within one year of the switch from conventional in-center hemodialysis. Converting to NHD is also associated with a strong trend towards improvement of diastolic dysfunction.

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INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of both hospitalization and mortality in patients on hemodialysis[1]. Left ventricular hypertrophy (LVH) is strongly linked to the subsequent development of cardiovascular morbidity and is highly associated with all-cause mortality[2]. For this reason, LVH is utilized as an acceptable surrogate outcome in hemodialysis studies[3-6]. At the initiation of dialysis, surveillance transthoracic echocardiography (TTE) has documented that over 70% of patients have LVH[7]. While patients on dialysis who have congestive heart failure (CHF) do have traditional CVD risk factors such as hypertension and diabetes, it has been suggested that there may be multifactorial explanations for their CHF beyond these traditional CHF risk factors[8]. Some of these include abnormal serum levels of electrolytes, proteins and lipids[8]; volume overload, uremia, anemia, acidosis, hyperparathyroidism[9], and sleep disorders[10].

Nocturnal home hemodialysis (NHD)

NHD is a form of renal replacement therapy in which patients perform hemodialysis overnight for a minimum of 6 hours per night, 5 or more nights per week. Extended hours hemodialysis has emerging evidence of superior efficacy over conventional hemodialysis (CHD) regimens of 4 hours of hemodialysis, 3 times per week, traditionally the standard of care in most contemporary dialysis units[11]. Extended hours hemodialysis is most conveniently performed in a patient's home, and has been shown to be at least cost-neutral, if not cheaper than facility-based CHD regimens[6]. A few previous studies have shown that NHD improves left ventricular mass, blood pressure control, mineral metabolism[3], uremia, anemia[12], albumin[13], and sleep disorders[10]. It is likely that improvements in at least some of these parameters in patients on NHD is related to a regression in LVH and thereby a reduction in mortality.

Echocardiography

Two-dimensional transthoracic echocardiography allows for the noninvasive assessment of left ventricular mass[14]. One observational study has suggested that NHD causes a sustained regression of LVH within one year, as assessed by echocardiography[4]. Echocardiography can also be used to measure diastolic dysfunction, which is associated with an increase in all-cause mortality[15]. Diastolic dysfunction is graded on a scale from 0 to IV. Grade 0 is considered to be normal function, whereas Grade IV represents the highest level of diastolic dysfunction, and is irreversible[16].

Cardiovascular Magnetic Resonance Imaging (CMR)

CMR is more precise than echocardiography for determining left ventricular parameters, including ventricular mass[17]. Specifically, CMR is used to measure left ventricular mass index

(LVMI) and left atrial volume index (LAVI). An increase in left ventricular mass is an independent predictor of both morbidity and mortality due to CVD[14]. Left atrial size is independently associated with all-cause mortality[18]. A randomized controlled trial has shown that NHD causes an improvement in left ventricular mass in as little as six months, as measured by CMR[3].

OBJECTIVES

The aim of this study is to determine whether NHD improves cardiac parameters within one year as compared to CHD as assessed by both echocardiography and CMR. We will also attempt to correlate changes in cardiac parameters with other variables such as medical history, blood pressure, lab values, medication use, and biomarkers. Patient self-reported quality of life will also be recorded to help quantify tolerability of this novel form of self-care dialysis.

METHODS

Patient Population

All patients being enrolled in the NHD training program at Seven Oaks General Hospital in Winnipeg, Manitoba were asked to participate in this study from program inception in January 2009 to 2011. Patient selection for the training program is based on a number of factors, such as ability to perform NHD (e.g. cognitive function, motor skills, adequate vision and ability to speak and understand English), availability of a reliable training and support partner, life expectancy > 12 months, and no reliable expectation of receiving a kidney transplant within 12 months. Each patient was sent for baseline and one-year on-treatment echocardiograms and CMRs. Each patient also served as their own control for the purpose of evaluating the cardiac parameters from this imaging. Patient flow through the study is summarized in Figure 1.

Upon enrolling in the NHD training program, patients received 6-10 weeks of dedicated training in the home hemodialysis unit 1:1 with a nurse. Training time was dependent upon the rate at which the patient was able to learn the skills necessary to safely perform NHD. After completing training, patients performed home hemodialysis during the day for 1-4 weeks before beginning overnight extended hours hemodialysis.

Extensive demographic, comorbidity, and medication data were collected at baseline. This information is summarized in Table 1. Monthly hematology and chemistry lab values, including pre- and post-NHD calcium and phosphate, were also recorded. Information regarding the amount and adequacy of NHD performed, as well as pre- and post-NHD blood pressures was

also recorded monthly. Every three months, parathyroid hormone and low-density lipoprotein levels were measured. Health Research Ethics Board Approval from the University of Manitoba was obtained for this study.

Echocardiography

All patients underwent baseline TTE at the time they began NHD. Follow-up echocardiography was performed 12 months after baseline. All echocardiograms were performed using a standard echocardiogram machine (GE Vivd 7, Milwaukee, WI, USA). Parasternal and apical views were used. Standard two-dimensional images were obtained. Spectral and color Doppler, and tissue Doppler imaging were performed. Echocardiographic analysis was conducted using dedicated computer software (EchoPAC, version 110.0.0, GE Medical, Milwaukee, WI, USA). Cardiac measurements including chamber dimensions and volumes, interventricular septal thickness, and posterior wall thickness were determined in accordance with the guidelines of the American Society of Echocardiography[19]. Transmitral left ventricular (LV) filling velocities at the tips of the mitral valve leaflets were obtained from the apical four-chamber view using pulsed-wave Doppler echocardiography. The transmitral LV filling signal was traced manually, and the following variables were obtained: peak early (E) and late (A) transmitral velocities, E/A ratio, and E-wave deceleration time. Tissue Doppler-derived indices were recorded at the lateral mitral annulus. These indices included systolic velocities (S'), early diastolic velocities (E'), and late diastolic velocities (A'). Finally, the dimensionless index of E/E' was calculated.

CMR

Baseline CMRs were performed on all patients at the time that NHD was started. One year later, patients underwent follow-up CMRs. All CMRs were performed using a 1.5 Tesla Siemens Scanner (Magnetom Sonata, Siemens Medical Systems, Erlangen, Germany). Analysis of all CMRs was performed using dedicated computer software (CMR42, version 1.0.0, Circle Cardiovascular Imaging, Calgary, AB, Canada). Cardiac measurements including chamber dimensions and volumes, interventricular septal thickness, and posterior wall thickness were determined in accordance with the guidelines of the Society for Cardiovascular Magnetic Resonance[20]. The left and right ventricular walls were traced manually at end-systole and end-diastole. Each slice that contained an appropriate view of the ventricle was used. The sum of these tracings provided the end systolic volume (ESV) and end diastolic volume (EDV) respectively. End diastole was defined as the slice in which the image was at its largest volume. End systole was defined as the slice in which the image was at its smallest volume. The difference between the EDV and ESV (EDV – ESV) was recorded as the stroke volume. Left and right ventricular mass were calculated using the summation of slices method[21]. To do this, manual tracing of the epicardial and endocardial borders was performed in each end-diastolic and end-systolic slice that was used to calculate EDV and ESV. These were then multiplied by slice thickness to determine myocardial volume at end-diastole and end-systole. Each volume was then multiplied by $1.05 g/cm^3$ to ascertain left and right ventricular mass.

Biomarkers

N-terminal pro-brain natriuretic peptide (NT-proBNP) was measured in samples of patient serum at baseline and every three months for one year using an electrochemiluminescence immunoassay (ECLIA).

Quality of Life

Patients also voluntarily provided quality of life data by completing the Kidney Disease Quality of Life-36 short form (KDQOL-36) and EuroQoL EQ-5D surveys at baseline and then every three months for one year from the completion of NHD training. The Visual Analogue Scale (VAS) portion of the EQ-5D is a quantitative measure of the patient's self-reported state of health.

Statistical Analysis

Paired two-tailed t-tests were used for LVMI, LAVI, and all other variables in Table 2 except for the following. A Wilcoxon Signed Ranks Test was used for diastolic dysfunction. A McNemar Test was used to determine if the change in phosphate binder use was statistically significant. A p-value of less than 0.05 was considered to be statistically significant for all tests.

RESULTS

Primary Outcome

Left ventricular mass index as determined by CMR decreased for all patients at one-year follow-up from a baseline of 35±2 to 33±2g/m^2 ($p<0.0009$) (Figure 2). Left atrial volume index also decreased for all patients at one-year follow-up, again as calculated from CMR images from 140±2 to 136±3mL/m^2 ($p<0.009$) (Figure 3). As measured by echocardiography, diastolic dysfunction improved in all patients except one. In this patient, diastolic dysfunction remained at the same grade. This resulted in a strong trend towards an overall improvement in diastolic dysfunction ($p=0.06$) (Table 3).

Secondary Outcomes

NHD improved pre-dialysis systolic blood pressure from a baseline value of 118±13 to a twelve-month follow-up value of 107±12 ($p<0.02$) (Figure 4). All other values shown in Table 2, including NT-pro-BNP (Figure 5), did not show a statistically significant improvement ($p>0.05$).

KDQOL-36 is a validated instrument for measuring health-related quality of life for patients undergoing dialysis, with results reported using five specific domains[22]. EQ-5D is another standardized instrument for measuring health outcomes[23]. Quality of life data as collected using the KDQOL-36 survey did not show a statistically significant change in either direction in any of

the five domains at any three-month interval when compared to baseline. Similarly, quality of life data obtained using the VAS portion of the EQ-5D survey also showed no statistically significant improvement or deterioration (Figure 6).

DISCUSSION

In the current study, we confirmed that NHD is associated with a statistically significant decrease in LVMI. To our knowledge, our study is the first to suggest that NHD also improves LAVI. We believe that our study is also the first to suggest that there is a strong trend towards improvement of diastolic dysfunction after conversion to NHD. Furthermore, NHD was shown in our study to have a positive effect on blood pressure.

Improvements in LVMI are important in the dialysis population because LVH affects 70% of this population group[7]. In addition, LVMI has been shown to be an independent prognostic marker for both cardiovascular events and mortality[24]. Previous studies have also shown that NHD causes a regression of LVH, as confirmed by calculating LVMI through measurements made on both echocardiography and CMR. Improvements in LVMI have been shown to have a mortality benefit[25]. This may occur through a few different mechanisms. LVH is associated with coronary ischemia, reduced cardiac reserve, myocardial infarction, arrhythmias, myocardial fibrosis, and diastolic dysfunction, all of which lead to poorer cardiac outcomes[24]. Regression of LVH is associated with a decreased rate of mortality in patients with end-stage renal disease (ESRD)[25]. Therefore, NHD may provide for a decrease in cardiovascular events and mortality.

LAVI is a marker of diastolic dysfunction[26]. It is currently unclear whether LAVI is only a marker of a patient's other cardiovascular risk factors, or whether it actually predisposes to cardiovascular events and mortality, rendering LAVI regression a potentially therapeutic target. An increased LAVI causes an increased rate of atrial fibrillation, so this may be a mechanism by which a large left atrium increases the risk of cardiovascular events and mortality[27]. On the other hand, LAVI may simply be a marker of hypertension[28] and diastolic dysfunction[29], which in themselves are cardiovascular risk factors. Regardless, the decrease in left atrial size seen in patients who undergo NHD may reduce their risk of cardiovascular events and mortality.

Similarly, diastolic dysfunction is also associated with an increased risk of cardiovascular events and all-cause mortality[15]. Diastolic dysfunction implies that there is a problem with relaxation, filling, or distensibility of the left ventricle during diastole. Diastolic dysfunction may result in an increased rate of cardiovascular events and mortality due to the interplay between LVH and myocardial ischemia. For a given degree of ischemia, diastolic dysfunction is increased in patients who have LVH as compared to patients who do not[30]. This may be because hearts with LVH may have decreased capillary growth[31], coronary perfusion pressure[32], and coronary flow

reserve[33]. In addition, these hearts may also have increased coronary atherosclerosis and coronary vascular compression, decreasing cardiac blood supply[32]. As such, the strong trend toward improvements in diastolic dysfunction which can occur when patients switch from CHD to NHD may decrease both cardiovascular events and mortality.

proBNP is a hormone released by the heart in response to high ventricular filling pressures due to heart failure[34]. proBNP is cleaved to form the active BNP and the inactive NT-proBNP. Almost all dialysis patients have NT-proBNP levels well above normal reference ranges[35]. This is due to a combination of volume overload causing heart failure and a decreased ability of the kidneys to excrete proBNP due to ESRD[36]. Our approach to NT-proBNP represents an attempt at a novel method of determining which patients will benefit the most from NHD. Namely, all five patients had improvements in cardiac parameters (LVMI, LAVI) but not all had improvements in NT-proBNP. We hope in future to be able to correlate these cardiac improvements with improvements in NT-proBNP or another biomarker.

Our results with regard to quality of life data are not surprising given our small study population size. A previous randomized controlled trial using a longer form of the KDQOL-36 instrument compared NHD to CHD and found an improvement in certain domains of quality of life. It also found an improvement from baseline to six month follow-up for NHD patients using the EQ-5D survey[3]. A systematic review of the effects of NHD also concluded that quality of life improved after conversion to NHD[37].

Our study did not concur with previous studies that demonstrated improvements in mineral metabolism. We expect that our results with regard to changes in lab values between baseline and one-year follow-up found few improvements because of our small study population size. The improvement in blood pressure supports previous studies that have shown similar outcomes[3]. A systematic review also found that blood pressure control was improved after switching to NHD[37]. However, it was unable to find a consensus on the effect of NHD on anemia and mineral metabolism[37].

Limitations

Although the current study supports the conclusions of previous studies and introduces several novel cardiovascular benefits of NHD, the results must be interpreted in light of its limitations. First, the study population size was small. This resulted in an inability to detect differences in quality of life data and lab values between baseline and one-year follow-up. Second, this was an observational cohort study. Performing a randomized controlled trial is the gold standard. However, there is currently a debate as to whether randomizing patients to what could potentially be considered to be an inferior renal replacement therapy modality is ethical[38]. A major factor in the success of a patient on NHD is their motivation to learn and perform independent dialysis. This type of patient is typically motivated by the desire to optimize their treatment, and reap the purported benefits of this therapy right away. This fact renders randomization of patients to

CHD or NHD a virtually impossible task, as the Frequent Hemodialysis Network investigators found in their RCT[5].

Future reports from this study will include a larger number of patients and additional biomarkers in an attempt to determine if there is a set of biomarkers that can accurately predict which patients will benefit most from NHD. Future studies should use hard endpoints such as cardiovascular events or mortality instead of surrogate markers like LVMI in order to accurately quantify the benefit of NHD over CHD.

CONCLUSIONS

NHD improves LVMI, LAVI, and blood pressure within one year of the switch from CHD. Converting to NHD is also associated with a strong trend towards improvement of diastolic dysfunction.

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Figure 1. Patient Flow Through the Study

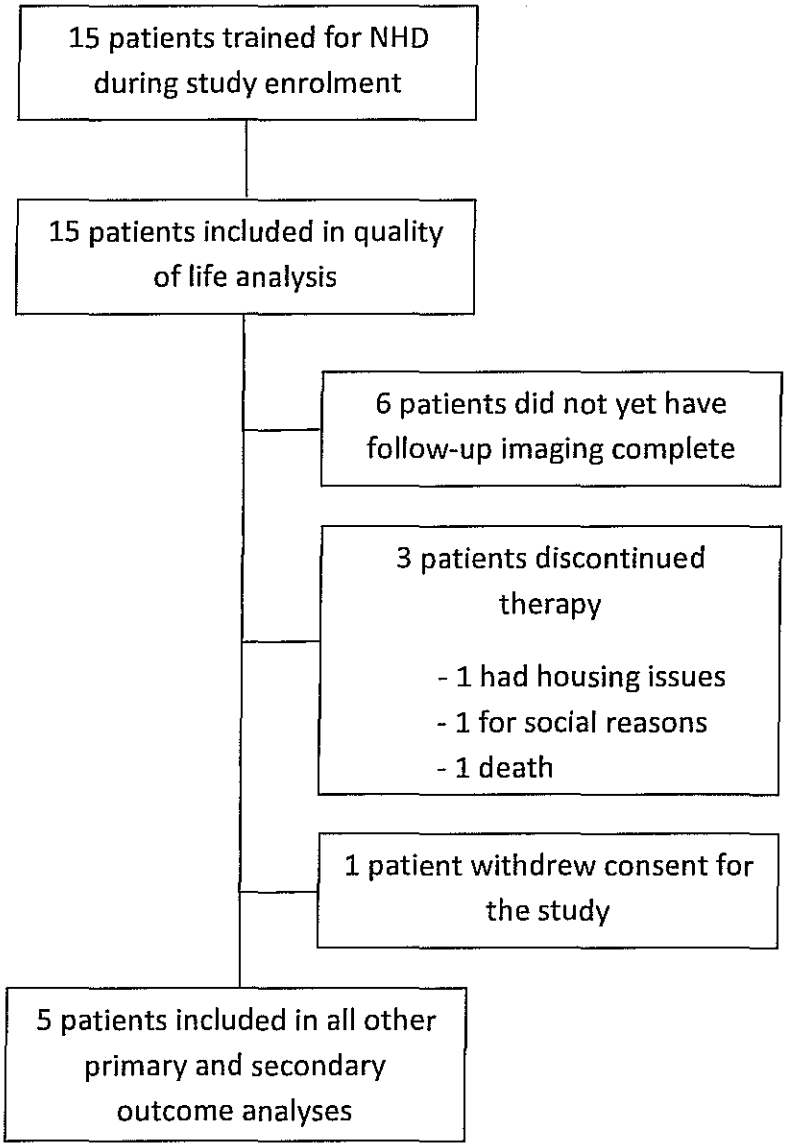

Table 1. Baseline Characteristics

Characteristic	Patient Population (n = 5)
Age, mean (SD), y	48.6 (17.5)
Male sex	2
Race	
Caucasian	4
Asian	1
Body mass index, mean (SD)	21.7 (4.0)
Time receiving dialysis, mean (range), y	10.6 (4-17)
Prior renal transplantation	3
Baseline dialysis modality	
In-center hemodialysis	5
Vascular access	
Arteriovenous fistula	4
Tunneled dialysis catheter	1
Cause of end-stage renal disease	
Glomerulonephritis	2
Polycystic kidney disease	2
Diabetic nephropathy	1
Comorbid illness	
Hypertension	3
Ischemic heart disease	2
Diabetes mellitus	1
Valvular heart disease	1
Arrhythmia	1
Smoking	1
Congestive heart failure	0
Cerebrovascular accident	0

Table 2. Outcomes for CMR, blood pressures, lab values, and medication use

Characteristic	Baseline	One-Year	Change	p value
Left ventricular mass index (LVMI), mean (SD), g/m^2	142 (2)	138 (3)	-4	p<0.0009
Left atrial volume index (LAVI), mean (SD), mL/m^2	35 (2)	33 (2)	-2	p<0.009
Pre-dialysis systolic blood pressure, mean (SD), mm Hg	118 (13)	107 (12)	-12	p<0.02
Post-dialysis systolic blood pressure, mean (SD), mm Hg	129 (19)	109 (16)	-20	p=0.09
Pre-dialysis diastolic blood pressure, mean (SD), mm Hg	74 (10)	67 (9)	-7	p=0.14
Post-dialysis diastolic blood pressure, mean (SD), mm Hg	73 (11)	67(11)	-6	p=0.34
Pre-dialysis serum calcium, mean (SD), mmol/L	2.48 (0.15)	2.36 (0.21)	-0.12	p=0.06
Post-dialysis serum calcium, mean (SD), mmol/L	2.37 (0.15)	2.32 (0.11)	-0.05	p=0.49
Pre-dialysis serum phosphate, mean (SD), mmol/L	1.32 (0.16)	1.25 (0.29)	-0.07	p=0.69
Post-dialysis serum phosphate, mean (SD), mmol/L	0.56 (0.11)	0.65 (0.19)	+0.09	p=0.48
Serum hemoglobin, mean (SD), g/L	112 (8)	113 (7)	+1	p=0.67
Serum ferritin, mean (SD), ug/L	509 (295)	324 (176)	-185	p=0.24
Serum albumin, mean (SD), g/L	40 (0)	40 (3)	0	p=1
Serum parathyroid hormone, mean (SD), ng/L	433 (339)	268 (275)	-165	p=0.44
Serum low-density lipoprotein, mean (SD), mmol/L	1.9 (1.0)	1.9 (0.5)	0	p=0.95
Serum NT-proBNP, mean (SD), ng/L	11889 (11538)	5909 (3880)	-5980	p=0.35
Patient weight, mean (SD), kg	59.3 (14.7)	60 (12.9)	+0.7	p=0.53
Weekly erythropoietin dose, mean (SD), IU	7000 (3162)	6000 (5612)	-1000	p=0.11
# of hypertensive drugs, mean (SD)	1 (1)	1 (1)	0	p=0.39
Use of phosphate binders, # using	3	0	-3	p=0.08

Figure 2. Left Ventricular Mass Index at baseline and one-year follow-up for each patient (n = 5)

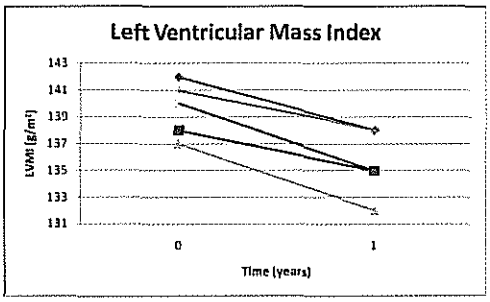

Figure 3. Left Atrial Volume Index at baseline and one-year follow-up for each patient (n = 5)

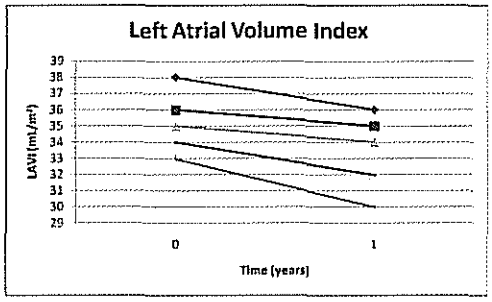

Table 3. Diastolic Dysfunction at baseline and one-year follow-up for each patient (n = 5)

Baseline Grade	Follow-up Grade
II	I
II	0
III	I
I	I
II	I
	p = 0.06

Figure 4. Pre-Dialysis Systolic Blood Pressure at baseline and one-year follow-up for each patient (n = 5)

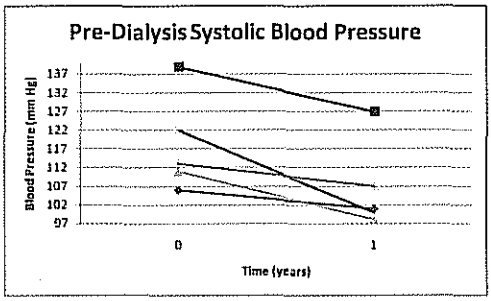

Figure 5. NT-proBNP at baseline and every three months for one year for each patient (n = 5)

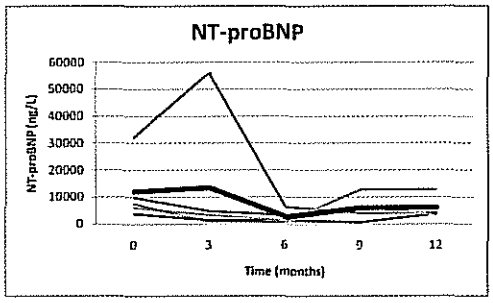

Figure 6. Quality of Life using KDQOL-36 and EQ-5D VAS at baseline and every three months for one year for each patient (n = 15)