Correlation between ultrafiltration rate and phase angle measured by BIA in chronic kidney disease patients on regular hemodialysis

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Abstract. Chronic Kidney Disease (CKD) patients with regular hemodialysis have high rates of morbidity and mortality that may be related to the hemodynamic effects of rapid UFR and low PhA value. In this study, we investigated whether high UFR is associated with a low value of PhA thus indirectly affect the risk of morbidity and mortality. UFR and Bioelectrical Impedance Analysis (BIA) examination on 92 subjects were recorded shortly after HD and analyzed by using Pearson correlation test. Multivariate analysis was also conducted to identify several factors that can affect the value of Phase angle. The number of HD regular CKD patients with PhA <4 based on the division of the UFR (cc/kg/h) <10, 10-13, ≥ 13, respectively were 3, 10 and 6, whereas patients with ≥ 4 PhA <10, 10-13, ≥ 13 respectively were 60, 11, and 2. The results showed a significant relationship between UFR with PhA. In CKD patients with regular HD, UFR has an inverse relationship with the value of PhA. UFR optimal value in patients with CKD with regular HD is <10 cc/kg/h.

1. Introduction
The rate of morbidity and mortality of patients with end-stage Chronic Kidney Disease (CKD) undergoing hemodialysis is still high, approximately 15-20 percent per year, despite improvements in cardiovascular disease management, infection and dialysis therapy.[1,2,3]

One of the potentially modifiable cardiovascular risk factors is the ultrafiltration rate (UFR, the rate at which fluid is removed during the dialysis process).[2] When normal kidney function is reduced, ultrafiltration will be required to maintain volume control (i.e., salt and water balance), but ultrafiltration can also simultaneously lead to non-physiological fluid shifts and hemodynamic instability.[2,4] In time, these factors may contribute to the incidence of tissue ischemia, maladaptive cardiac structural changes, arrhythmias, and sudden cardiac death.[2,5]

Bioelectrical Impedance Analysis (BIA) is an easy-to-use, non-invasive, repeatable device that does not rely on operators with low error rates, and therefore reliable results can be obtained to measure nutritional status in patients undergoing dialysis on a regular basis.[6-8] One of the parameters that can be assessed from this BIA check is the phase angle (PhA). As an indicator of the fluid distribution between intracellular and extracellular, the phase angle is also the most sensitive indicator of malnutrition.[9-11] In dialysis patients, there may be a reduction in the mass and integrity of cell membranes and fluid imbalances, so that the phase angle values will be low. Phase angle is also
used as a prognostic marker in some circumstances where cell integrity and fluid balance are disrupted, such as HIV infection, cancer, cirrhosis of the liver, pregnant women, sepsis, and hemodialysis. [7,12-14] We conducted this study to clarify the correlation between UFR and Phase angle as a prognostic marker in some circumstances where cell integrity and fluid balance were impaired in patients with end-stage renal disease undergoing hemodialysis twice a week.

2. Methods
This study was an observational study with analytic cross-sectional measurement. The research was conducted in hemodialysis unit of Adam Malik Hospital Medan. Sampling was obtained from May 2014 to July 2014 with the approval of FK USU Research Ethics Committee.

The target population was CKD patient with hemodialysis (≥ 3 months) at Haji Adam Malik Hospital Medan. With the following admission criteria, i.e., patients with hemodialysis, regularly undergoing hemodialysis (≥3 months), age ≥ 17 years, willing to participate and sign an informed consent in the study from May 2014 to July 2014.

Exclusion criteria were subjects/patients with AV fistula attached to both arms, patients with HIV, cancer, cirrhosis of the liver, pregnant women, and sepsis.

All subjects included in the study were carried out the recording of name, age, sex, height, CKD etiology, duration of HD, pre-dialysis Bodyweight (BW) and post-dialysis BW, and recording of UFR values for each CKD patient undergoing regular hemodialysis, and BIA examination by means of the Maltron brand BIA after completion of a hemodialysis session to obtain a phase angle value.

The basic population characteristic data was shown in tabulation with a description of each parameter. Chi-square test was used to compare two nominal data variables. Anova tests were used to compare more than 2 groups of normally distributed data, while the Willis-Kruskal test for non-distributed data was normal. To see UFR Correlation and Phase angle, we used Pearson correlation test. Multivariate analysis was also done to see some factors that could affect the value of Phase angle. Data were processed with computer statistics. All statistical tests were considered meaningful if the value of p < 0.05. Ethical clearance (permission to conduct research) was obtained from the Research Committee of the Medical Field Faculty of Medicine, University of North Sumatra.

3. Results
Overall, a total of 92 patients with the chronic renal disease who underwent hemodialysis over 3 months were included in this study. The demographic, clinical and bioelectric characteristics of population studies had been summarized. (Table1)

| Characteristics | n = 92 |
|-----------------|-------|
| Age             | 48.83 (12) |
| Gender/sex, n (%) |       |
| Men             | 57 (62) |
| Women           | 35 (38) |
| Height, mean (SD), cm | 161.74 (7) |
| Body Weight, mean (SD), kg | 60.25 (11.84) |
| Body Mass Index, mean (SD), kg/cm² | 22.19 (4.04) |
| BIA             |       |
| TBW (lt)        | 32.97 (6.31) |
| ECW (lt)        | 16.44 (6.07) |
| ECW/TBW         | 0.49 (0.12) |
| ECW/ICW         | 1.16 (0.86) |
| BCM (kg)        | 23.24 (4.49) |
| Dry.Wgt (kg)    | 56.73 (12.02) |
| PhA, mean (SD), ° | 5.15 (1.52) |
| Etiology        |       |
| Non DM          | 71 (77.2) |
| DM              | 7 (7.6) |
In this cross-sectional study, 92 patients with the majority of male subjects were 57 (62%); average age 48.83 years (SD = 12 years). The average height and weight of the respondents were 161.74 cm (SD = 7 cm) and 60.25 kg (SD = 11.84 kg), IMT 22.19 kg/cm².

Based on the etiology, as many as 71 people (77.2%) subjects had chronic kidney disease due to Non-DM, with the percentage of hypertension as etiology was as many as 60 people (65.2%) of the total number of subjects. While the number of patients with the etiology of DM was as many as 21 people (22.8%) of the total number of subjects. Research subjects with etiology of DM and hypertension were found as many as 14 people (15.2%). The results also showed that the subjects had performed hemodialysis with PhA <4 based on UFR group division (cc/kg/h) <10, 10-13, ≥ 13, respectively were 60 (82.2%), 11 (15.1%), and 2 (2.7%). Through the results obtained from this study, it could be concluded that the optimal ultrafiltration rate in patients with chronic kidney disease with regular hemodialysis is <10 cc/kg/hour. There was a significant difference to UFR values based on PhA (p = 0.0001). Differences in UFR values could also be found based on the etiology of CKD (p = 0.002) (Table 2).

From the results of this study, the number of chronic renal disease patients undergoing regular hemodialysis with PhA <4 based on UFR group division (cc/kg/h) <10, 10-13, ≥ 13, respectively were 3 people (15.8% ), 10 (52.6%), and 6 (31.6%), whereas in patients with PhA ≥ 4 on the UFR group (cc/kg/h) <10, 10-13, ≥ 13, respectively were 60 (82.2%), 11 (15.1%), and 2 (2.7%). Through the results obtained from this study, it could be concluded that the optimal ultrafiltration rate in patients with chronic kidney disease with regular hemodialysis is <10 cc/kg/hour. There was a significant difference to UFR values based on PhA (p = 0.0001). Differences in UFR values could also be found based on the etiology of CKD (p = 0.002) (Table 2).

Table 2. Differences in BMI, age, PhA, gender, duration of HD and CKD etiology based on UFR (cc/kg/h).

| Variable                                      | < 10 (n=63) | 10-13 (n=21) | ≥ 13 (n=8) | P     |
|-----------------------------------------------|-------------|--------------|------------|-------|
| Body Mass Index, mean (SD), kg/cm²            | 22.58 (4.18) | 22.21 (3.55) | 19.09 (3.15) | 0.069a |
| Age, mean (SD), year                          | 48.43 (12.63) | 51.38 (10.51) | 45.25 (10.42) | 0.396b |
| PhA                                           |             |              |            |       |
| < 4                                           | 3 (15.8)    | 10 (52.6)    | 6 (31.6)   | 0.0001c |
| ≥ 4                                           | 60 (82.2)   | 11 (15.1)    | 2 (2.7)    |       |
| TBW (lt)                                      | 32.52 (5.72) | 34.55 (7.78) | 32.35 (6.78) | 0.690b |
| ECW (lt)                                      | 14.67 (4.12) | 19.82 (8.27) | 21.52 (6.48) | 0.0001b |
| ECW/TBW                                       | 0.45 (0.08) | 0.56 (0.11)  | 0.66 (0.12) | 0.0001b |
| ECW/ICW                                       | 0.90 (0.59) | 1.50 (0.96)  | 2.29 (1.19) | 0.0001b |
| BCM (kg)                                      | 24.05 (4.34) | 22.54 (4.12) | 18.69 (3.99) | 0.004a |
| Dry.Wgt (kg)                                  | 58.71 (11.82) | 55.38 (11.13) | 44.75 (9.09) | 0.006a |
| Gender/sex                                    |             |              |            |       |
| Men                                           | 44 (69.8)   | 11 (19.3)    | 2 (3.5)    | 0.029c |
| Women                                         | 19 (54.3)   | 10 (28.6)    | 6 (17.1)   |       |
| Hemodialysis duration, mean (SD), month        | 22.35 (18.9) | 14.48 (12.32) | 16.88 (24.1) | 0.068b |
| Etiology                                      |            |              |            |       |
| Non DM                                        | 56 (78.9)   | 10 (14.1)    | 5 (7)      | 0.002d |
| DM                                            | 3 (42.9)    | 3 (42.9)     | 1 (14.3)   |       |
| DM and Hypertension                           | 4 (6.3)     | 8 (57.1)     | 2 (14.3)   |       |

aKruskal Wallis  
bChi Square  
cAnova  
dChi Square

From the results of this study, the number of chronic renal disease patients undergoing regular hemodialysis with PhA <4 based on UFR group division (cc/kg/h) <10, 10-13, ≥ 13, respectively were 3 people (15.8% ), 10 (52.6%), and 6 (31.6%), whereas in patients with PhA ≥ 4 on the UFR group (cc/kg/h) <10, 10-13, ≥ 13, respectively were 60 (82.2%), 11 (15.1%), and 2 (2.7%). Through the results obtained from this study, it could be concluded that the optimal ultrafiltration rate in patients with chronic kidney disease with regular hemodialysis is <10 cc/kg/hour. There was a significant difference to UFR values based on PhA (p = 0.0001). Differences in UFR values could also be found based on the etiology of CKD (p = 0.002) (Table 2).
meant that the obtained regression line equation could explain 28.7% PhA variation, the rest was explained by other factors. The statistical test results had meaningful correlation and showed a moderate correlation between UFR with PhA.

| Table 3. Linear correlation and linear regression analysis of UFR and PhA. |
|-----------------|---------|----------------|----------------|
|                 | r       | $R^2$          | Linear Equation |
| UFR             | -0.536  | 0.287          | 7.193 – 0.239 (UFR) |
| P               | 0.0001  |               |                 |

To know the influence of BMI, etiology, gender, and age to PhA, we used multiple linear regression tests in this research because PhA’s variable was numerical variable. Using the backward method as presented in Table 4, the variables which could predict PhA was UFR and etiology. The equation, obtained from multiple linear regression models, for predicting PhA was as follows:

\[ y = 7.089 – 0.196 \times \text{UFR} – 0.685 \times \text{etiology} \]

From ANOVA’s test result on model 5, we obtained p-value = 0.0001 (p < 0.05). It had been concluded that the above equation was feasible to predict the value of PhA. Adjusted R square value of 0.39 or 39% implied that the obtained equation was able to explain the PhA of 39%, while the remaining 61% was explained by other variables which were not examined in this study.

| Table 4. Multivariate analysis of factors related to PhA. |
|-----------------|--------|----------------|----------------|
| Model           | B      | Std. Error     | p       | R       | Adjusted R square | F      | P      |
| Constanta       | 7.089  | 0.341          | 0.000   | 0.624   | 0.390             | 28.401 | 0.0001 |
| UFR             | -0.196 | 0.039          | 0.000   |         |                  |        |        |
| Etiology        | -0.685 | 0.177          | 0.000   |         |                  |        |        |

4. Discussion

Although the biological correlations between dialysis Ultrafiltration Rate (UFR) and Phase Angle (PhA) to mortality and morbidity had been investigated and correlated significantly, the correlation between ultrafiltration rate and Phase Angle alone had not been previously described in existing literature. In this study, for the first time, we conducted a study that searched for a correlation between dialysis Ultrafiltration Rate with Phase Angle.

Previous analysis study of Flythe et al showed significant associations between cardiovascular mortality and ultrafiltration rate >13 ml/kg/h and indicated that the risk of cardiovascular death would begin to increase as ultrafiltration rate exceeded 10 ml/kg/hr. Study results by Maggiore et al. described an increased risk of death with low Phase Angle in 131 patients with end-stage renal disease. Furthermore, Chertow et al.’s study identified the Phase Angle value below 4 degrees would increase the risk of death.

The results of this study showed the number of patients with chronic renal disease who undergone regular hemodialysis with PhA <4 based on the group division UFR (cc/kg/h) <10, 10-13, ≥ 13, with each sequence, were 3 people (15.8%), 10 (52.6%), and 6 (31.6%), whereas in patients with PhA ≥4 on the UFR group (cc/kg/h) <10, 10-13, ≥ 13, respectively were 60 (82.2%), 11 (15.1%), and 2 (2.7%) with p value 0.0001. From this results, we could conclude that the higher the value of UFR in patients with chronic kidney disease with regular hemodialysis, the lower the PhA values would be obtained from this patient. Thus it also implied that high UFR values would have an impact which was not good in patients with regular hemodialysis, given the results of previous studies had shown a significant correlation between low PhA values with high morbidity and mortality rates, both in terms of cardiovascular and overall mortality rates.

The correlation between higher UFR, lower PHA value and an increased cardiovascular morbidity and mortality and overall should not be surprising. During dialysis, the fluid is drawn directly from the vascular space, when the withdrawal of dialysis and resorption of other compartments, the volume of
circulation will decrease, and organ disorders (especially cardiovascular) may occur. This effect is reinforced by the limitation of cardiac reserves and autonomic dysfunction, which both are common finding among hemodialysis patients.[15]

From the results of statistical analysis, this study also found a significant correlation between UFR and PhA, with moderate correlation strength ($r = -0.536$). After a multivariate analysis of factors correlated with PhA, the results showed that UFR and etiology of late-stage CKD had a strong relationship with PhA ($R = 0.624$ composite of both factors ($p = 0.0001$). Some studies showed that PhA inversely proportional to age and significantly lower in women, whites and diabetic patients.[16,17]

The phase angle parameter is an indicator of the health of body cells, cell hydration and the integrity of cell membranes. Research on HD patients showed a positive linear correlation between phase angle with nutritional status and patient life expectancy. A low phase angle value indicates the cell's inability to store energy and cell damage markers.[18]

There are two options for minimizing UFR in current clinical practice: (1) limiting the patient's fluid intake and (2) allowing more time for fluid withdrawal (i.e., prolonging dialysis time). Clinical experience and published data suggested that interventions aimed at reducing patient fluid intake interdialysis were often ineffective.[10,19] In addition, in Chertow et al.'s analysis showed that larger ultrafiltration rates were correlated (i.e., adjusted) with increased interdialysis (IDWG) weight, suggesting that a more gradual fluid volume withdrawal would yield better results regardless of the amount of weight gain itself. In practice today, the length of the dialysis session is determined by the index of small molecules (e.g., urea) clearance; UFRs are adjusted to allow for the additional drawdown of fluid that was required in this fixed time allotment. In addition, UFRs may be minimized with more frequent dialysis frequency (which also minimizes accumulation of fluid that increases with time).[20,21]

The strength of this study included careful data collection, the sample size which was not small in number. The weaknesses of this study included cross-sectional analysis, which also had the potential for residual confounding factors and bias. To minimize the risk of residual confounding factors, this study performed a multivariate analysis that was adjusting for estimated confounding variables which were correlated with UFR and PHA, such as age, sex, comorbid conditions, dialysis vascular access type, and use of antihypertensive medication. However, this study could not rule out the possibility of remaining confounding factors which were associated with those baseline variables or other variables that were not considered. The second weakness was that the UFR value used in this study was an observational value on the place without considering the patient's UFR values in the previous dialysis so that patients with unstable interdialysis weight gain would have an effect on the change in median UFR values during dialysis. Finally, this study excluded patients <17 years old, limiting the generalization of the results of this study to this subpopulation.

5. Conclusion
In conclusion, this research study showed that among patients with the chronic renal disease with regular HD, ultrafiltration rate had a correlation that was inversely related to the value of phase angle. Even after multivariate analysis, the results showed that UFR and HD etiology still significantly influenced the value of phase angle. And the optimal ultrafiltration rate in patients with the chronic renal disease with regular hemodialysis was < 10 cc/kg/hr.

References
[1] The United Renal Data System 2010 Overall hospitalization and mortality Am. J. Kidney Dis. 55(1) S1-7
[2] Flythe J E, Kimmel S E and Brunelli S M 2011 Rapid fluid removal during dialysis is associated with cardiovascular morbidity and mortality Int. Soc. Nephrol. 79 250-7
[3] Lowrie E and Lew N 1990 Death risk in hemodialysis patients: the predictive value of commonly measured variables and an evaluation of death rate differences between facilities Am. J. Kidney Dis. **15** 458-82

[4] Suharjono and Susalit E 2009 Hemodialisis *Buku ajar ilmu penyakit dalam* vol 1, ed A W Sudoyo, B Setiyohadi, *et al.* (Jakarta: Pusat Penerbitan Departemen Ilmu Penyakit Dalam FKUI) pp 1050-2

[5] Holmberg B and Stegmay B G 2009 Cardiovascular conditions in hemodialysis patients may be worsened by extensive interdialytic weight gain Hemodialysis Int. **27**–31

[6] Ursula G K 2004 Bioelectrical impedance analysis – part I: review of principles and methods *Clin. Nutr.* **23** 1226-43

[7] Saxena A and Sharma R K 2008 Role of bioelectrical impedance analysis (BIA) in renal disease *Indian J. Nephrol.* **15** 194-7

[8] Donadio C, Consani C, Ardini M, Bernabini G, Caprio F, Grassi G, Lucchesi A and Nerucci B 2005 Estimate of body water compartments and of body composition in maintenance hemodialysis patients: comparison of single and multifrequency bioimpedance analysis J. Ren. Nutr. **15**(3) 332-44

[9] Bernard C 2007 Fluid balance, dry weight and blood pressure in dialysis *Hemodialysis Int.* **11** 21-31

[10] Chertow G M, Jacobs D O, Lazarus J M, Lew N L and Lowrie E G 1997 Phase angle predicts survival in hemodialysis patients *Nat. Kidney Foundation* **7**(4) 204-7

[11] Abad S, Sotomayor G, Vega A, Perez de Jose A, Verdalles U, Jofre R and Lopez-Gomez J M 2011 The phase angle of electrical impedance is a predictor of long-term survival in dialysis patients *Nefrologia* **31**(6) 55-68

[12] Oliveira G, Santos A P and Mello E D 2012 Bioelectrical impedance phase angle: utility in clinical practice *Int. J. Nutr.* **5**(3) 123-7

[13] Anees M 2004 Evaluation of nutritional status of patients on hemodialysis *J. Coll. Physic. Surg. Pak.* **14**(11) 665-9

[14] Gupta D, Lammersfeld C A, Burrows J L, Dahlk S L, Vashi P G, Grutsch J F, Hoffman S and Lis C G 2004 Bioelectrical impedance phase angel in clinical practice: implication for prognosis in advanced colorectal cancer Am. J. Clin. Nutr. **80** 1634-8

[15] Stegmay B G 2003 Ultrafiltration and dry weight—what are the cardiovascular effects? *Artificial Organs* **27**(3) 227–9

[16] Steiber A L, Zadeh K K, Seeker D, McCarthy M, Sehgal A and McCann L 2004 Subjective Global Assessment in chronic kidney disease: A review J. Ren. Nutr. **14**(4) 191-200

[17] Steiber A L, Leon J B, Seeker D, Mc Carthy M, Mc Cann L, Serra M, Sehgal A R and Kalantar-Zadeh K 2007 Multicenter study of the validity and reliability of subjective global assessment in the hemodialysis population J. Ren. Nutr. **17** 336–42

[18] Dumler F A 2010 Low bioimpedance phase angle predicts a higher mortality and lower nutritional status in chronic dialysis patients J. Phys. **224**

[19] Jaeger J Q and Mehta R L 1999 Assessment of dry weight in hemodialysis: an overview J. Am. Soc. Nephrol. **10** 392–403

[20] Flythe J E, Curhan G C and Brunelli S M 2012 Shorter length dialysis sessions are associated with increased mortality, independent of body weight Kidney Int. **83** 104-13

[21] Chazot C and Jean G 2009 The advantages and challenges of increasing the duration and frequency of maintenance dialysis sessions *Nat. Clin. Pract. Nephrol.* **5**(1) 34-44