Resistant Hypertension in Hemodialysis Patients

Authors
Ahmad B. Elden¹, Walaa H. Mohamad², Muhammad Hosam Magraby³
¹,³Critical Care Unit, Assiut University, ²Nephrology Unit, Assiut University
Corresponding author
Ahmad B. Elden
Assiut University, P.O. Box 71111 Assiut, Egypt
Telephone: +20-1009820300, Fax: +20-2333327
Email: ahmadbahie@yahoo.com

Abstract
Objectives: This study aimed to assess prevalence of resistant hypertension (RHT) in hemodialysis (HD) patients.

Patients and Methods: We conducted a cross sectional study on 135 HD patients. RHT was defined as failure to reach target blood pressure (BP) control (systolic BP <140 mmHg and diastolic BP < 90 mmHg) with maximal dose of 3 antihypertensive therapies (AHT) including diuretics in patients with good daily urine output (> 500 cc/day) or at least 2 L/session ultrafiltration volume in oliguric (<500-100 cc/day) or anuric patients (< 50 cc /day). Patients with post HD hypertension underwent 24h ambulatory monitor for their BP, which hourly measured their BP.

Results: In our study; 34 (25.2%) of patients were non hypertensives, 43 (31.8%) were controlled hypertensives, 58 (43.0%) were uncontrolled hypertensives. Uncontrolled hypertensives with inadequate AHT were 53 (39.2 %), where RHT patients were 5 (3.7%)of all study population.

Conclusions: We concluded that RHT had3.7% prevalence in HD patients.

Keywords: resistant hypertension, haemodialysis.

Introduction
Hypertension is a major contributor toexcessive cardiovascular morbidity and mortality in in hemodialysis (HD) patients because it is a cause as well as a consequence ofchronic kidney disease (CKD) and end-stage renal disease (ESRD)¹. Multiple mechanisms are likely involved in blood pressure dysregulation in HD patients and some of them have resistant hypertension (RHT), defined as BP that remains above goal despite treatment with 3 different classes of AHT agents. One of the 3 agents should be a diuretic and all agents should be prescribed at optimal dose amounts or controlled hypertension with at least 4 drugs². Aggressive control of hypertension in dialysis is mandatory. Antihypertensive therapy (AHT) in HD patients was associated with a reduced risk of cardiovascular events, all-cause mortality, and

Ahmad B. Elden et al JMSCR Volume 04 Issue 06 June
cardiovascular mortality[3]. HD provides better volume control in ESRD patients by achieving patient’s dry weight. However, clearly defined guidelines are not available for hypertensive patients in the HD population and nearly 50-60% of HD patients continue to suffer from HTN[4] despite multiplicity of AHT. RHT is estimated to affect 15% to 30% of patients with essential hypertension[5]. The prevalence of RHT in dialysis patients is still unidentified. Our aim of this study was to study the prevalence of RHT in HD patients.

Patients and methods
We conducted a cross-sectional study, carried out on 135 patients who undergo regular HD in the Dialysis Unit of Assiut University Hospital in 2015. Written consents were obtained from most of the participants; illiterate participants gave their consent by finger prints. The study was approved by the ethical committee of Faculty of Medicine in Assiut University. Blood pressure was measured by well calibrated mercury sphygmomanometers in 3 different haemodialysis sessions, half an hour before, one hour during and half an hour after session. Recruited patients on AHT instructed to take their medications at night and to collect their urine output in sterile secured bottles. We used JNC 7 criteria for diagnosis of hypertension with systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg. Patients with post dialysis hypertension underwent 24h ambulatory monitor for their BP using Del Mar Reynolds/England S.N; 00008970, which hourly measured their BP. Maximal, minimal systolic and diastolic BPs were calculated. Night non dipper patients were identified. RHT was defined as failure to reach target BP control (systolic BP < 140 mmHg and/or diastolic BP < 90 mmHg) with maximal dose of 3 medications including diuretics in patients with good daily urine output (> 500 cc/day) or at least 2 L/session ultrafiltration volume in oliguric (<500-100 cc/day) or anuric patients (< 50 cc/day).

Classification of patients
We classified our recruit according to their hypertension state into 3 groups; non hypertensives (NonHTN) with pre, intra and post dialysis BP < 140 mmHg and diastolic BP < 90 mmHg) without AHT, controlled hypertensives (CHTN) with pre, intra and post dialysis BP < 140 mmHg and diastolic BP < 90 mmHg) with AHT, and uncontrolled hypertensives groups (UCHTN) with pre, intra and post dialysis BP ≥ 140 mmHg and or diastolic BP ≥ 90 mmHg) with AHT. UCHTN was sub classified into UCHTN with inadequate AHT (less than 3 AHT) and RHT as previously defined.

Statistical analysis
The statistical analysis was performed using SPSS (version 16.0, SPSS Inc., Chicago, IL, USA). The Kolmogorov–Smirnov test will be used to test normally. The continuous variables were presented as the means ± SD and categorical variables were presented as percentages. Student T test was used to compare between means of 2 continuous variables, ANOVA test was used to compare between means of > 2 continuous variables, and chi square test was used to compare percentages and ratios. A p-value < 0.05 was considered statistically significant.

Results
Basal characteristics
The study was carried out on 135 regular HD patients. 34 (25.2%) of patients were NonHTN, 43 (31.8%) were CHTN, 58 (43.0%) were UCHTN (Figure 1). There were insignificant differences between groups as regard age, gender, BMI, apparent aetiology of ESRD and duration of dialysis (Table 1). There were insignificant differences between CHTN and UCHTN groups in duration of hypertension. CHTN had significantly higher urine output than UCHTN.
Table (1): Demographic, Selected Clinical and Laboratory Characteristics of Patients

| CHARACTERISTICS         | Non HTN (n=34) | CHTN (n=43) | UCHTN (n=58) | P Value |
|------------------------|----------------|-------------|--------------|---------|
| AGE (YEARS)            | 42.35 ± 15.46  | 43.60 ± 12.89 | 42.41 ± 13.55 | 0.396   |
| MALE N (%)             | 20 (58.8%)     | 24 (55.8%)  | 24 (41.4%)   | 0.187   |
| BMI                     |                |             |              |         |
| Underweight N (%)      | 6 (17.6%)      | 2 (4.7%)    | 3 (5.2%)     | 0.064   |
| Normal weight N (%)    | 18 (52.9%)     | 22 (51.2%)  | 30 (51.7%)   | 0.988   |
| Overweight N (%)       | 7 (20.6%)      | 9 (20.9%)   | 11 (19.0%)   | 0.966   |
| Obese N (%)            | 3 (8.8%)       | 10 (23.3%)  | 14 (24.1%)   | 0.169   |
| Etiology               |                |             |              |         |
| Diabetes N (%)         | 7 (20.6%)      | 13 (30.2%)  | 24 (41.4%)   | 0.112   |
| Hypertension N (%)     | 0 (0.0%)       | 6 (14.0%)   | 4 (6.9%)     | 0.066   |
| CIN N (%)              | 21 (61.8%)     | 18 (41.9%)  | 22 (37.9%)   | 0.074   |
| Others N (%)           | 6 (17.6%)      | 6 (14.0%)   | 8 (13.8%)    | 0.865   |
| Duration of dialysis(YEARS) | 5.81 ± 4.40 | 5.30 ± 4.09 | 4.10 ± 3.17 | 0.087   |
| HB (g/dl)              | 10.5±2.39      | 11.0±3.15   | 10.1±2.22    | 0.453   |
| Serum Ca (mg/dl)       | 8.1±2.08       | 8.6±2.13    | 8.3±1.52     | 0.314   |
| Serum phosphate (mg/dl)| 4.0±0.72       | 3.9±0.91    | 4.0±0.69     | 0.608   |
| PD BUN (mg/dl)         | 55.3±55.30     | 53.9±7.2    | 55.0±0.02    | 0.355   |

NonHTN; non hypertensives, CHTN; controlled hypertensives, UCHTN; uncontrolled hypertensives, BMI: body mass index, ESRD: end stage renal disease, CIN: chronic interstitial nephritis, CIN included; chronic pyelonephritis, obstructive uropathy, analgesic nephropathy, reflux nephropathy, others included; ADPKD, chronic GN, and SLE, PN BUN; post dialysis Blood Urea Nitrogen

There were insignificant differences between groups in rate and amount of ultrafiltration. CHTN had significantly lower BP measurements (pre, intra and post dialysis) and lower numbers of AHT than UCHTN group.

Uncontrolled hypertensives with inadequate AHT were 27 (46.6%) with only one AHT and 26 (44.8%) with two AHT, with a total of 53 (91.4%) of UCHTN and 39.2 % of all study population. RHT patients were 5 (3.7%) of all study population (Figure 1).

Figure 1: distribution of hypertensive state

Figure 2: comparing post dialysis BP in urine output groups
There were insignificant differences between uncontrolled hypertensives with inadequate AHT and RHT regarding: mean of maximal systolic pressure, mean of minimal diastolic pressure, mean of minimal systolic pressure, mean of maximal diastolic pressure, mean of minimal systolic pressure, mean of minimal diastolic pressure (Figure 3) and non-dipper state (Not shown).

**Table (2): Hypertension duration, urine output, ultrafiltration characters and drug therapies**

| CHARACTERISTICS            | CHTN (n=34) | UCHTN (n=58) | P-value |
|----------------------------|-------------|--------------|---------|
| DURATION OF HTN (YEARS)    | 7.58 ± 5.62 | 7.38 ± 7.34  | 0.881   |
| URINE OUTPUT               |             |              |         |
| Anuric                     | 19 (44.2%)  | 31 (53.4%)   |         |
| Oliguric                   | 12 (27.9%)  | 23 (39.7%)   | 0.016   |
| Good                       | 12 (27.9%)  | 4 (6.9%)     |         |
| ULTRAFILTRATION            |             |              |         |
| UHVOLUME                   | 3.00 ± 0.67 | 3.38 ± 0.92  | 0.253   |
| PRE DIALYSIS               |             |              |         |
| Systolic BP (mmhg)         | 125.58 ± 19.25 | 148.71 ± 25.44 | 0.000   |
| Diastolic BP (mmhg)        | 77.33 ± 18.72 | 85.86 ± 13.93 | 0.010   |
| INTRA DIALYSIS             |             |              |         |
| Systolic BP (mmhg)         | 121.40 ± 13.55 | 151.64 ± 20.42 | 0.000   |
| Diastolic BP (mmhg)        | 74.65 ± 17.91 | 88.79 ± 11.41 | 0.000   |
| POST DIALYSIS              |             |              |         |
| Systolic BP (mmhg)         | 116.28 ± 9.77 | 153.79 ± 19.52 | 0.000   |
| Diastolic BP (mmhg)        | 70.00 ± 8.73  | 90.26 ± 10.61 | 0.000   |
| NUMBER OF DRUGS            |             |              |         |
| One Drug                   | 32 (74.4%)  | 27 (46.6%)   | 0.015   |
| Two Drugs                  | 8 (18.6%)   | 26 (44.8%)   |         |
| Three Drugs                | 3 (7.0%)    | 5 (8.6%)     |         |

ANURIC: < 100 cc/day, OLGURIC: 500-100 cc/day and GOOD: > 500cc/day.

**Urine output and post dialysis BP**

By pooling both CHTN and UCHTN groups, there was a significant trend of post dialysis BP to be reduced as urine output increase (Figure 2).

**Discussion**

Our study groups were homogenous in age, gender, apparent aetiology of ESRD, duration of dialysis and duration of hypertension which reduced confounding factors. Although rate and volume of ultrafiltration had insignificant differences between CHTN and UCHTN, urine output was significantly higher in CHTN, which may emphasize the importance of residual renal function (RRF) in BP control. RRF has been found to be important in maintaining fluid balance of BP: blood pressure, MAX: maximum, Sys: systolic, MIN: minimal, Dias: diastolic
HD patients. In the CANUSA Study, urine volume was a strong independent predictor of survival. Every 250 ml/min urine output was associated with a 36% reduction in overall mortality[6]. Loss of RRF is independently associated with suboptimal blood pressure control, likely a result of chronic volume expansion[7]. The severity of left ventricular hypertrophy (LVH), a strong independent predictor of mortality in dialysis patients, inversely correlates with the presence of RRF[8]. In addition, loss of RRF is associated with more severe anemia, hypoalbuminemia, and higher arterial pressure[9]. Patients on HD can preserve RRF and achieve better control of their BP by using synthetic membranes and ultrapure dialysis water, routine use of ACEIs and ARBs unless contraindicated, avoid use of non-steroidal anti-inflammatory drugs, oral phosphate solutions, and prolonged aminoglycoside antibiotics, intravenous contrast[10].

In our study survey; we found that inadequate control of hypertension had a more significant prevalence in HD patients than RHT, where HD with inadequate AHT accounted for 53 (39.2%) of all study populations and RHT patients were 5 (3.7%) of all hemodialysis study population and 5 (8.6%) of UCHTN. Urine output was significantly higher in CHTN, which may emphasise the importance of RRF in BP control.

### Conclusion

We concluded that inadequate control of hypertension had a more significant prevalence in HD patients than RHT, where UCHTN with inadequate AHT accounted by 53 (39.2%) of all study populations and RHT patients were 5 (3.7%) of all hemodialysis study population and 5 (8.6%) of UCHTN. Urine output was significantly higher in CHTN, which may emphasise the importance of RRF in BP control.

### Study limitations

We recruited only Caucasian patients, which may limit extrapolation to other ethnic groups. Moreover, our results apply only to HD patients under regular tertiary care. The small number of RHT made statistical difficulties to compare between them and UCHTN. We recommend the development of a well definite AHT protocols in managing hypertension in HD to aid in decreasing prevalence of uncontrolled hypertension.

### Acknowledgements

The authors wish to acknowledge Dr. Abdel Mohsen Abdelhie, Mr. Asmaa Abdellatif and Mr. Mohamoud in the dialysis unit for their contribution in gathering data and follow up of patients.

### Conflict of interests

The authors declare that there was no conflict of interests as regard the publication of this paper.

### References

1- Venkata C., RamS. and Andrew Z. Fenves: Management of Hypertension in Hemodialysis Patients. Current Hypertension Reports 2009, 11:292–98

2- Calhoun DA, Jones D, Textor S, et al: Resistant hypertension: diagnosis, evaluation, and treatment. A scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Hypertension
3- Heerspink HJL, Ninomiya T, Zoungas S, de Zeeuw D, Grobbee DE and Jardine MJ, et al: Effect of lowering blood pressure on cardiovascular events and mortality in patients on dialysis: A systematic review and meta-analysis of randomised controlled trials. Lancet 2009; 373: 1009-15.

4- Henrich WL and Lionel U. Mailloux: In: Schwab SJ, et al. eds. Hypertension in hemodialysis patients. Waltham, MA: Up to Date 2013.

5- Daugherty S.L., Powers J.D. and Magid D.J: Incidence and prognosis of resistant hypertension in hypertensive patients. Circulation 2012; 125:1635-42.

6- Bargman JM, Thorpe KE and Churchill DN: Relative contribution of residual renal function and peritoneal clearance to adequacy of dialysis: a reanalysis of the CANUSA study. Journal of American Society of Nephrology 2001, 12 (10): 2158-62.

7- Konings CJ, Kooman JP, Schonck M, Struijk DG, Gladziwa U, Hoornije SJ, van der Wall Bake AW, van der Sande SJ and Leunissen KM: Fluid status in CAPD patients is related to peritoneal transport and residual renal function: Evidence from a longitudinal study. Nephrology Dialysis Transplant 2003; 18(4): 797-803.

8- Wang AY, Wang M, Woo J, Lam CW, Lui SF, Li PK and Sanderson JE: Inflammation, residual renal function, and cardiac hypertrophy are interrelated and combine adversely to enhance mortality and cardiovascular death risk of peritoneal dialysis patients. Journal of American Society of Nephrology 2004, 15(8): 2186-94.

9- Pecoits-Filho R, Heimburger O, Barany P, Barany P, Suliman M, Fehrman-Ekholm I, Lindholm B and Stenvinkel P: Associations between circulating inflammatory markers and residual renal function in CRF patients. American Journal of Kidney Disease 2003; 41(6): 1208-12.

10- Jeffrey Thomas and Isaac Teitelbaum: Preservation of Residual Renal Function in Dialysis Patients. Advances in Peritoneal Dialysis 2011; 27.

11- Rahman M, Dixit A, Donley V, Gupta S, Hanslik T, Lacson E, Ogundipe A, Weigel K and Smith MC: Factors associated with inadequate blood pressure control in hypertensive hemodialysis patients. American Journal of Kidney Disease 1999, 33(3):498-506.

12- Nabela Enam, Kavita Kakkad, Akshay Amin and Carole Lever: Management of hypertension in the hemodialysis population: a review of the literature. Journal of Community Hospital Internal Medicine Perspectives. 2014; 4(3): 10.3402/jchimp.v4.24055.