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The Open Urology & Nephrology Journal

Content list available at: www.benthamopen.com/TOUNJ/

DOI: 10.2174/1874303X01811010060, 2018, *11*, 60-71

RESEARCH ARTICLE

Excessive Ultrafiltration During Hemodialysis Plays a Role in Intradialytic Hypertension Through Decreased Serum Nitric Oxide (NO) Level

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Received: May 30, 2018 Revised: August 13, 2018 Accepted: August 17, 2018

Abstract:

Background:

Intradialytic hypertension is one of many complications during Hemodialysis (HD). The mechanism of intradialytic hypertension is currently unclear.

Objective:

This research aims to understand the association between excessive Ultrafiltration (UF) and intradialytic hypertension episode and its relationship with changes in endothelin-1 level (ET-1), Asymmetric Dimethylarginine (ADMA) level and Nitric Oxide (NO) level during HD.

Methods:

This study utilized a case-control design. A sample of one hundred and eleven patients who were already undergoing maintenance HD for more than three months was included. Serum levels of NO, ET-1, and ADMA were examined before and after HD; samples were followed by as much as six times consecutive HD session, in which ultrafiltration and blood pressure during HD were noted.

Results:

From 112 samples obtained, 32.1% (36/112) had intradialytic hypertension. Using regression analysis, we found a significant association between changes in NO levels and intradialytic hypertension. We found a significant association between excessive UF and intradialytic hypertension (p=0.001), adjusted OR=5.17. Path analysis showed the existence of a significant relationship between UF volume during HD and intradialytic hypertension (CR 5.74; p<0.01), as well as a significant relationship between UF volume during HD and NO levels (CR -3.70: p<0.01). There was a direct relationship between NO serum levels with intradialytic hypertension (CR -7.08: p<0.01).

Conclusion:

Excessive UF during HD plays a role in intradialytic hypertension episode through decreased NO serum levels. There was no clear role of ADMA and ET-1 serum levels on intradialytic hypertension episode.

Keywords: Hemodialysis, Intradialytic hypertension, Ultrafiltration, NO, ADMA, ET-1.

1. INTRODUCTION

Hemodialysis (HD) remains as one of the management procedures in order to substitute a part of the renal function.

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This action is routinely performed in patients with stage V Chronic Kidney Disease (CKD) or Chronic Renal Failure (CRF) [1]. It was estimated that there were 116,395 people in the United States with a new incidence of CRF in 2009 and more than 380,000 patients with CRF undergo regular hemodialysis [2]. While in Indonesia, 15,353 patients underwent HD in 2011. The number rose up as many as 4,268 people in 2012, resulting in 19,621 new patients on HD [3].

During HD, several patients still experiencing medical problems although a new system and HD equipment have been developed. Hemodynamic disturbances are a frequent complication in patients undergoing HD [1, 4]. Blood pressure decreases with Ultrafiltration (UF) or withdrawal of fluids while on HD. Intradialytic hypotension occurs in 20-30% of patients undergoing regular HD [5]. However, in some people, the problem that occurs is intradialytic hypertension. Intradialytic hypertension, defined as an increase in systolic BP during HD, is a relatively common problem observed in about 5-15% of the maintenance HD population [6 - 8]. It is currently receiving attention since the occurrence of intradialytic hypertension would affect the adequacy of HD and mortality [8]. Several elements were suggested to cause intradialytic hypertension, *i.e.*, Renin-Angiotensin-Aldosterone System (RAAS) activation due to hypovolemia, ultrafiltration (UF) duration, excess activity of sympathetic nervous system, K^+ and Ca^{2+} variation during HD, fluid overload, Erythropoietin (EPO) therapy-induced increased of blood viscosity, rise in Cardiac Output (COP), omission of antihypertensive medications during HD and vasoconstriction due to endothelin-1 (ET-1) [1].

Ultrafiltration is performed during HD to remove excess fluid in the blood. Excessive UF during HD will cause many problems in both hemodynamic parameters as well as cardiovascular disorders [9]. During UF, hypovolemia will occur, which in turn will stimulate the RAAS activity and could cause intradialytic hypertension episode [10]. In a study comparing 30 patients with intradialytic hypertension to 30 controls, hypertension-prone patients exhibited an increase in systemic vascular resistance and a significant decrease in nitric oxide levels about endothelin-1 at the end of HD [11].

The activity of endothelial cells has an important role in the variation of blood pressure during HD. The most important vasoactive agents are nitric oxide (NO): a smooth muscle vasodilator; asymmetric dimethylarginine (ADMA): an endogenous inhibitor of nitric oxide synthase; and endothelin-1 (ET-1): a potent vasoconstrictor. These substances have a substantial effect on sympathetic activity, peripheral vasoconstriction and blood pressure control in particular, including intradialytic hypertension [12]. There are differences in changes in NO and ET-1 levels during HD between the control group and the hypertension-prone group. At the end of HD, patients with intradialytic hypertension exhibited a significant increase in ET-1 levels and a significant reduction in the ratio of NO/ET-1 levels compared to the control group [11]. Another study also found that individuals with intradialytic hypertension showed a significant increase in ET-1 levels after HD [13].

The studies above indicated that there is an interaction between endothelial dysfunction with intradialytic hypertension episode; however, the cause of the occurrence of endothelial dysfunction in patients with intradialytic hypertension is not entirely understood. The pathophysiology, mechanisms and appropriate therapeutic strategies for intradialytic hypertension episode remain unclear. This study was therefore designed to find a relationship between excess UF on HD with intradialytic hypertension episodes through the involvement of endothelial dysfunction. Endothelial dysfunction is characterized by an increase in the concentration of ET-1 or elevated levels of ADMA or decreased serum levels of NO during HD.

2. MATERIALS AND METHODS

2.1. Study Design

This was a case-control study which investigated the relationship between UF volume during HD and the incidence of intradialytic hypertension, as well as the relationship between changes in serum levels of ET-1, NO, and ADMA before and after HD with UF volume on HD. This study was conducted in Sanglah Hospital Hemodialysis Unit, in Denpasar, from August to November 2012. The minimum required samples in this study be 110 people for both study groups.

The independent variables in this study were UF volume, and changes in serum levels of NO, ET-1, and ADMA. The dependent variable was intradialytic hypertension. While the control/confounding variables were age, gender, renal disease, comorbidities, medications, HD factors (dialysate, HD session, HD vintage therapy, and KT/V), and membrane factors (surface area, volume priming, UF coefficient, *in-vitro* clearance).

Excessive ultrafiltration is defined as an amount of fluid drawn by the HD machine during an HD session more than 4.8% of dry BW (*e.g.*,> 3.4 kg in patients with dry BW 70 kg). Serum level of ADMA was measured with a *quantitative sandwich enzyme immunoassay* (ELISA) in µmol/l, before and after HD, using reagent Cat. No. 17 EA 201-96 Biorad Product. Intradialytic hypertension defined as an increase in systolic blood pressure after HD ≥10 mmHg compared with TDS before HD, at least four times out of 6 consecutive HD sessions. Blood pressure was measured with a mercury sphygmomanometer and performed by trained nurses in a hemodialysis unit. All patients signed written informed consent, which describes the detail of the study and the content was subject to publication, prior to the study.

2.2. Statistical Analysis

Descriptive analysis was used to describe the general characteristics and frequency distribution of various variables. Logistic regression analysis was used to calculate the odds ratio of the following variables: UF, changes of NO, ADMA and ET-1 before and after HD to intradialytic hypertension; and to adjust the confounding variables on the relationship. Estimated odds ratios *(odds ratio*/OR) were presented in the form of 95% confidence interval. Path analysis was conducted to assess the influence/effect of the independent variable against the dependent variable as the outcome—direct relationship between UF and intradialytic hypertension as well as the indirect relationship between UF and intradialytic hypertension through changes in the serum levels of NO, ADMA, ET-1 during HD. Statistical analysis was conducted using $p<0.05$ as the limit of significance and by using SPSS statistical software.

3. RESULTS

One hundred twelve subjects were included and observed. Study subjects had an average age of 44 years, approximately 54.5% (61/112) were men. Overall, 32.1% (36/112) had intradialytic hypertension.

3.1. Characteristics of the Data

The baseline characteristics of the study subjects are presented in Table **1**. The mean age of patients was 43.75 ± 9.39 years. Dialysis was performed for 34.75 ± 30.51 months. The major cause of the end-stage renal disease was chronic pyelonephritis. Mean hemoglobin level was 8.34 ± 1.40 g/dl. Mean serum albumin level was 3.87 ± 0.54 mg/dl. Most patients used ACE inhibitors as an antihypertensive agent, and only 16.8% of patients used erythropoietin to maintain hemoglobin level.

Table 1. The baseline characteristics of the study subjects with and without intradialytic hypertension.

Characteristics	Intradialytic hypertension (n = 36) mean ± SD	No intradialytic hypertension (n = 76) mean ± SD	P value
Age (years)	43.2 ± 9.54	43.7 ± 9.38	0.92
Gender (%)			
Male	47.2	57.9	0.42
Female	52.8	42.1	
Duration of HD (months)	34.50 ± 33.15	34.86 ± 29.4	0.78
Etiology (%)			
Chronic pyelonephritis	61.1	57.9	0.75
Chronic glomerulonephritis	38.9	39.5	
Nephrosclerosis	-	-	
Hemoglobin (g/dl)	8.2 ± 1.6	8.3 ± 1.31	0.43
Serum albumin (mg/dl)	3.9 ± 0.6	3.8 ± 0.53	0.60
CaP product	56.27 ± 18.30	54.8 ± 17.3	0.49
Dry body weight (kg)	54.34 ± 13.35	56.4 ± 10.48	0.15
Body mass index ($kg/m^{2)}$	22.26 ± 4.37	22.61 ± 3.5	0.59
Anti-hypertensive agents (%)			
ACE inhibitors	69.4	66.7	0.31
CCBs	11.1	9.7	0.59
Beta blockers	22.2	38.9	0.00
Clonidine	30.6	27.8	0.45
ARBs	19.4	13.9	0.12
Erythropoietin therapy (%)			

(Table 1) contd.....

Characteristics	Intradialytic hypertension (n = 36) mean ± SD	No intradialytic hypertension (n = 76) mean ± SD	P value
Yes	16.7	16.7	0.90
No	50.6	13.3	

3.2. Blood Pressure Profile During Dialysis

Blood pressure profile of the sample can be seen in Table **2**.

Table 2. Blood pressure profile of subjects with and without intradialytic hypertension.

HD session	Blood pressure	Pre-HD				Post-HD			
		Group		Group difference	P value	Group		Group difference	P value
		IDH (Mean ± SD	Non-IDH (Mean ± SD)			IDH (Mean ± SD	Non-IDH (Mean ± SD)		
HD-1	Systolic	142.5 ± 22.89	143.28 ± 24.02	-0.79	0.87	147.2 ± 24.56	144.21 ± 21.92	3.01	0.52
	Diastolic	84.72 ± 10.27	85.65 ± 9.42	-0.10	0.95	88.33 ± 12.07	85.65 ± 8.3	2.68	0.17
HD-2	Systolic	140.55 ± 23.89	142.10 ± 9.42	-1.55	0.73	148.05 ± 23.52	144.73 ± 21.25	3.31	0.46
	Diastolic	84.72 ± 10.27	86.84 ± 9.26	-2.12	0.28	87.22 ± 10.31	86.97 ± 8.48	0.25	0.89
HD-3	Systolic	141.38 ± 19.29	141.97 ± 23.36	-0.58	0.89	148.05 ± 20.67	141.57 ± 19.73	6.48	0.11
	Diastolic	85.5 ± 12.05	85.52 ± 9.14	0.02	0.98	87.5 ± 12.27	86.84 ± 8.82	0.66	0.75
HD-4	Systolic	138.05 ± 21.20	141.28 ± 24.54	-3.13	0.51	140.55 ± 30.75	140.15 ± 25.86	0.39	0.94
	Diastolic	85.27 ± 10.27	85.92 ± 11.33	-0.64	0.77	86.38 ± 8.3	86.97 ± 10.58	-0.58	0.77
HD-5	Systolic	143.33 ± 29.17	141.44 ± 22.43	1.89	0.71	144.44 ± 23.83	140.92 ± 20.86	3.52	0.42
	Diastolic	85.83 ± 8.74	85.13 ± 10.39	0.70	0.72	87.22 ± 10.03	87.10 ± 10.04	0.11	0.95
HD-6	Systolic	138.33 ± 20.77	139.34 ± 20.74	-1.00	0.81	146.66 ± 24.14	138.55 ± 19.03	8.11	0.05
	Diastolic	83.33 ± 9.85	85.13 ± 8.71	-1.79	0.33	86.66 ± 9.56	85.52 ± 8.06	1.14	0.51
Means	Systolic	140.69 ± 16.69	141.55 ± 16.97	-0.86	0.80	145.83 ± 18.52	141.69 ± 16.11	4.14	0.23
	Diastolic	85.04 ± 6.49	85.70 ± 6.13	-0.65	0.60	87.22 ± 8.22	86.51 ± 5.71	0.72	0.59

3.3. Ultrafiltration Profile

During observation for six consecutive HDs, UF volume was recorded. The average UF volume performed can be seen in Fig. (**1**).

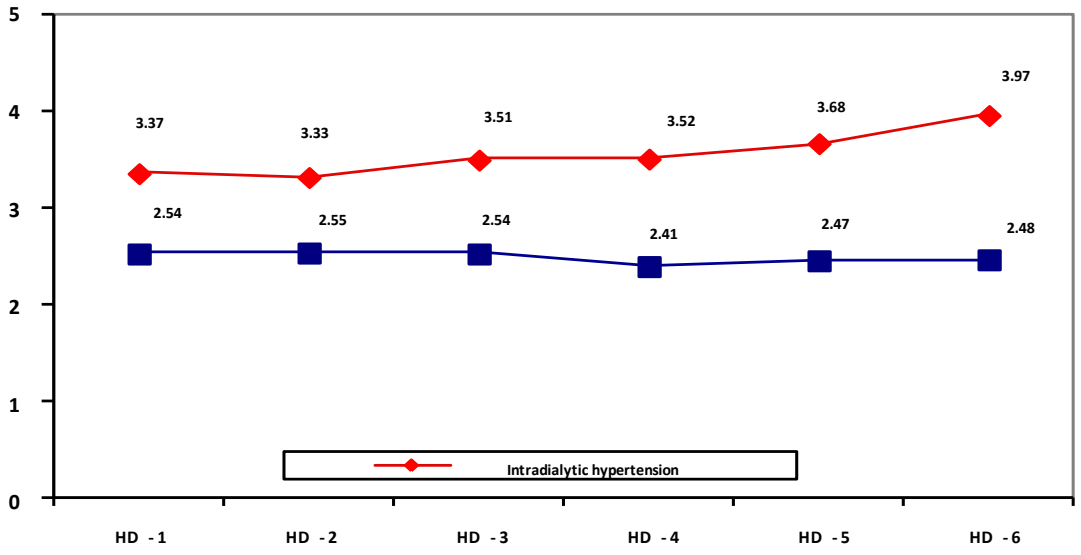

Fig. (1). Average ultrafiltration volume during hemodialysis.

3.4. Changes in Serum Levels of Na, K, and Ca During HD

Changes in Serum Levels of Na, K, and Ca of the sample during HD can be seen in Table **3**.

Table 3. Sodium, potassium and calcium levels before and after dialysis.

–	IDHt Group (Mean ± SD)			Non-IDHt Group (Mean ± SD)			Group Difference	P value
	Pre-HD	Post HD	Difference (post-pre HD)	Pre-HD	Post HD	Difference (Post-pre HD)		
Natrium (mmol/L)	136.33 ± 2.62	137.08 ± 3.98	0.75 ± 3.75	135.84 ± 2.76	136.22 ± 3.61	0.38 ± 3.78	0.37	0.63
Kalium (mmol/L)	5.58 ± 0.97	3.49 ± 0.87	-2.08 ± 1.04	5.11 ± 0.80	3.40 ± 0.60	-1.70 ± 0.85	-0.38	0.05
Calcium (mol/dL)	8.92 ± 0.94	11.03 ± 1.08	2.1 ± 1.49	9.13 ± .05	10.61 ± 1.07	1.47 ± 1.46	0.63	0.03

3.5. Changes in Serum Levels of NO, ADMA, and ET-1 During HD

Table **4** shows that there was a decrease of NO serum levels (mean ± SD) after HD in both the groups, and this reduction was greater in the intradialytic hypertension group compared to the non-intradialytic hypertension group (-9.8 ± 4.79*vs.* -4.22 ± 2.77 μM, p-value = 0.0). A different phenomenon was observed in ADMA level parameter; in the intradialytic hypertension group, there was a decrease in post-HD ADMA serum level, whereas in the non-intradialytic hypertension group, there was an increase in post-HD ADMA serum level (-0.33 ± 0.22 *vs.* 0.27 ± 0.20 μm/L, respectively). However, the difference in ADMA levels was not significant (p-value >0.05). There was an increase in ET-1 serum concentrations in both the groups (0.18 ± 0.41 *vs.* 0.18 ± 0.70 pg/ml). However, this increase did not differ significantly between the groups (p-value >0.05).

Table 4. NO, ADMA, and ET-1 serum levels before and after dialysis.

Serum levels	IDHt Group (Mean ± SD)			NonIDHT Group (Mean ± SD)			Group Difference	P value
	Pre-HD	Post HD	Difference (Post-pre HD)	Pre-HD	Post HD	Difference (Post-pre HD)		
NO (μM)	13.62 ± 5.47	3.80 ± 1.4	-9.8 ± 4.79	8.15 ± 3.27	3.93 ± 2.22	-4.22 ± 2.77	-5.59	0.0
ADMA (μm/L)	0.81 ± 0.23	0.47 ± 0.14	-0.33 ± 0.22	0.78 ± 0.24	0.95 ± 0.51	0.27 ± 0.20	-0.06	0.16
ET-1 (pq/ml)	2.14 ± 1.25	2.37 ± 1.12	0.18 ± 0.41	2.39 ± 1.19	2.58 ± 1.35	0.18 ± 0.70	0.00	0.99

3.6. The Relationship Between Changes in the Levels of NO, ET-1, and ADMA with Intradialytic Hypertension

Table **5** shows that the coefficient regression of NO, UF volume, and excessive UF have a significance level of <0.001; this value is much less than 0.05. The research hypothesis stating that NO, UF volume and excessive UF have a significant effect on intradialytic hypertension was accepted. Unadjusted OR value of NO and UF volume was 0.59 and 4.28, respectively. This meant that if the other independent variables remain unchanged, then any increase in 1 μmol/L of NO will cause intradialytic hypertension incidence by 59% or any increase in 1 liter UF is likely to cause 4.28 times of intradialytic hypertension event. This influence remained significant after controlling for confounding variables, such as the amount of antihypertensive medications taken and changes in Na and Ca levels during HD (adjusted OR for NO = 0.6; 95% CI 0.49 to 0.73, p = 0.001, adjusted OR for UF volume = 5.17; 95% CI 2.64 to 10.11, p = 0.001, and adjusted OR for excessive UF = 167.19; 95% CI 27.56 to 1,013.91, p = 0.001).

Table 5. The relationship between NO, ADMA, as well as ET-1 serum levels, UF volume, and intradialytic hypertension events.

Independent Variables	Unadjusted OR	95% CI	P value	Adjusted OR	95% CI	P value
NO (Increasing each 1 μm/L)	0.59	0.48-0.72	0.00	0.60	0.49-0.73	0.00
ADMA (Increasing each 1 μm/L)	0.26	0.04-1.67	0.16	0.15	0.02-1.19	0.07
ET-1 (Increasing each 1 pg/ml)	1.00	0.53-2.89	0.99	0.94	0.49-1.794	0.85
UF volume (Increasing each 1 liter)	4.28	2.41-7.62	0.00	5.17	2.64-10.11	0.00
Excessive UF (UF volume > 4.8% of dry weight) increasing each 1%	100.45	21.05-479.33	0.00	167.19	27.56-1013.91	0.00

Description:
Adjusted with
1. Amount of anti-hypertensive agents consumed.
2. Difference in sodium levels before and after HD.
3. Difference in calcium levels before and after HD.

The coefficient regression of ADMA had a significance level of 0.16; this value was greater than 0.05. The research hypothesis which stated that ADMA has a significant effect on the intradialytic hypertension was rejected. The same result was seen in the serum levels of ET-1. The coefficient regression of ET-1 had a significance level of 0.99; this value is above 0.05. The research hypothesis stating ET-1 has a significant influence on the intradialytic hypertension was also rejected.

3.7. Path Analysis

To see the causal effect of changes in NO, ET-1, and ADMA levels, UF volume during HD and intradialytic hypertension episode, we performed path analysis. Exogenous variables were: NO, ADMA, ET-1 and UF volume; endogenous variables were intradialytic hypertension events.

Based on Fig. (**2**), the direct effect on intradialytic hypertension was obtained as follows: effect of UF volume on intradialytic hypertension was 0.16 (16%); the effect of NO levels on intradialytic hypertension was 0.05 (5%); the effect of ET-1 levels on intradialytic hypertension was 0.02 (2%); the effect of ADMA levels on intradialytic hypertension was 0.11 (11%). Furthermore, the direct effect of UF volume on other variables was as follows: UF effect on NO was 1.37 (137%); the effect of UF on ADMA was 0.03 (3%); the effect of UF on ET-1 was 0.06 (6%). It was clear that UF had the strongest effect on NO, whereas the variable that was most strongly affecting intradialytic hypertension was UF. The parameter most strongly affecting intradialytic hypertension was the cumulative effects of UF (24%).

3.8. Relationships Between Constructs

After analysis of AMOS relationships between constructs can be seen in Table **6**. There was a significant association between UF volume and NO (CR -3.70, $p < 0.01$). A significant relationship was also seen between UF volume and intradialytic hypertension (CR 5.74, $p < .01$). Moreover, there was a significant association between NO and intradialytic hypertension (CR -7.08, $p < 0.01$). In addition, there was no significant relationship between UF volume and ADMA levels, between UF volume and ET-1 levels, between ET-1 levels and intradialytic hypertension, as well as between intradialytic hypertension and ADMA levels.

Table 6. Relationship between two variables constructs.

No.	Variables	Regression weight			Standardize regression weight
		Estimate	CR	p	
1	Vol. UF → ADMA	-0.26	-1.35	0.18	-0.13
2	Vol. UF → ET-1	0.04	0.70	0.48	0.07
3	Vol. UF → NO	-1.23	-3.70	***	-0.34
4	Vol. UF → HID	0.18	5.74	***	0.40
5	NO → HID	-0.06	-7.08	***	-0.49

(Table 5) contd.....

No.	Variables	Regression weight			Standardize regression weight
		Estimate	CR	p	
6	ET-1 → HID	-0.02	-0.25	0.80	0.02
7	ADMA → HID	-0.14	-0.97	0.33	-0.06

Table **7** shows that UF volume had the most powerful effect and direct effect on the incidence of intradialytic hypertension. Table **8** demonstrates the relationship between UF volume as an independent variable and ADMA, NO and ET-1 levels as dependent variables.

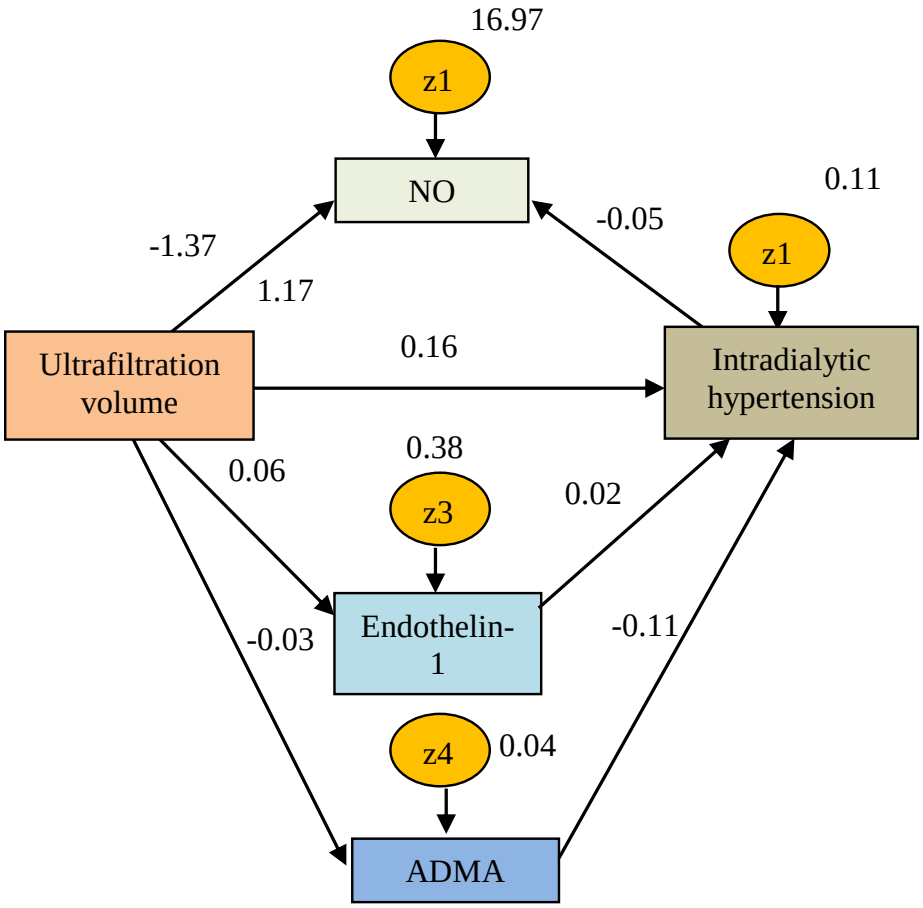

Fig. (2). Pathway analysis of independent variable to dependent variable.

Table 7. Relationships between various variables and intradialytic hypertension.

Effect(s)	NO levels → intradialytic hypertension	ET-1 levels → intradialytic hypertension	ADMA levels → intradialytic hypertension	UF volume → intradialytic hypertension
Total effect	-0.05	-0.02	-0.12	0.24
Direct effect	-0.05	-0.02	-0.12	0.16
Indirect effect	0.00	0.00	0.00	0.07

Fig. (**2**) and Table **8** show that there was a significant direct relationship between UF volume and intradialytic hypertension (CR 5.74, p <0.01, direct effect 16% and total effect 24%). There was a significant relationship between UF volume and NO (CR -3.70, p <0.01, direct effect was 137%). Moreover, there was a direct relationship between NO and intradialytic hypertension (CR -7.08, p <0.01, and the immediate effect was 5%).

Thus it could be said that UF and NO had significant effects on intradialytic hypertension. NO had the most substantial effect on intradialytic hypertension (CR -7.08) compared with UF (CR 5.74). Meanwhile, UF also had a significant effect on NO (CR -3.70). We concluded that there was an indirect relationship between UF volumes and intradialytic hypertension through changes in serum levels of NO.

Table 8. Relationship between independent and dependent variables.

Effect	UF volume → NO levels	UF volume → ADMA levels	UF volume → ET-1 levels	UF volume → intradialytic hypertension
Total effect	-1.37	-0.03	0.06	0.24
Direct effect	-1.37	-0.03	0.06	0.16
Indirect effect	0.00	0.00	0.00	0.07

4. DISCUSSION

Intradialytic hypertension is a common complication in patients undergoing regular HD. The authors found that nearly one-third of patients undergoing regular HD experience intradialytic hypertension. The mechanism of intradialytic hypertension is yet unclear, making it difficult for the management of intradialytic hypertension and subsequently causing inadequate dialysis. Research conducted by Inrig *et al.,* found that patients with regular HD experience association between intradialytic hypertension and endothelial dysfunction [14]. Our research supported the findings that proved the existence of a relationship between decreased NO serum levels and intradialytic hypertension events. A reduction in NO serum levels showed the involvement of endothelial dysfunction in intradialytic hypertension events. The findings of this study proved the association between excessive UF during HD with a subsequent decrease in NO levels and the incidence of intradialytic hypertension. In this study, we also found a direct relationship between UF volume and intradialytic hypertension as well as an indirect relationship between UF volumes and intradialytic hypertension through decreased NO serum levels.

This study found that the characteristics of subjects with intradialytic hypertension were not much different from non-intradialytic hypertension, but the intradialytic hypertension group had lower dry BW than the control group. A study conducted in 1995 found that patients who were prone to blood pressure increase during UF tend to overhydrate and suffer from cardiac dilatation [15]. A cohort study conducted by Inrig in 2009 found that patients with intradialytic hypertension had lower dry BW, increased interdialytic BW, lower serum albumin, and lower phosphorus level than patients who did not suffer from intradialytic hypertension [8].

The proportion of intradialytic hypertension events in patients with regular HD is not known [16]. Previous studies reported the incidence in varying amounts. Later on, this proportion is likely to increase. This study found that the incidence of intradialytic hypertension was 32.1%. Another study reported that the incidence of intradialytic hypertension was approximately 5-15% in patients undergoing regular HD. A cohort study conducted in 1748 defined intradialytic hypertension as an increase in post-dialysis BP of more than ten mmHg which was observed in 3 consecutive HD sessions. This study found that 12.2% of patients experienced intradialytic hypertension [8]. A retrospective cohort study on 22,955 HD sessions revealed that the prevalence of intradialytic hypertension was 21.3 per 100 HD sessions, with a median percentage of 17.8% [17]. Another study conducted in 2012 by Rubinger *et al.* reported a high incidence of intradialytic hypertension, as high as 52% (57/108). In this study, the term intradialytic hypertension was applied if there is an increase in post-dialysis SBP of ≥10 mmHg, or if there is hypertension that is resistant to UF that occurs after HD [16]. The difference in prevalence may be due to differences in methods of observation and definitions used for intradialytic hypertension. One of the difficulties in defining intradialytic hypertension stems from the lack of blood pressure targets on HD. Thus this issue is still being debated [18].

This study found that the mean pre-HD NO serum level on intradialytic hypertension group was higher than the control group. Post-HD NO serum level was decreased in both groups. However, the intradialytic hypertension group had a greater reduction compared to the control group. These findings resembled the results obtained in the study by Chou *et al.* in 2006, which found that NO levels were significantly higher in the group that was prone to hypertension. They also found a decrease in post-HD NO concentrations in both groups, with NO reduction occurring in much greater scale in the hypertensive group compared to the control group [11].

Nitric oxide is a natural antagonist of catecholamines. Nitric oxide is synthesized by the enzyme nitric oxide synthase (NOS), released by endothelial cells into the circulation. *In vitro* studies showed that NOS activity increases when blood is exposed to the membrane dialyzer [19]. With the discovery of the relationship between the serum levels of NO with intradialytic hypertension events, our study supported the results of previous studies. Chou *et al.* compared 30 patients with intradialytic hypertension and 30 controls to investigate the systemic vascular resistance. In hypertension-prone patients, there was an increase in systemic vascular resistance and a significant decrease in NO level about the ET-1 level at the end of HD [11].

Nitric oxide is formed at various locations. In CKD patients, endothelial dysfunction is characterized by decreased NO production by endothelial cells. This study also supports the theory that one of the many intradialytic hypertension mechanisms is due to endothelial dysfunction which is marked by decreased NO serum levels.

The decline in serum levels of NO in patients with intradialytic hypertension and the relationship between NO and intradialytic hypertension events demonstrate the role of endothelial dysfunction in the pathogenesis of intradialytic hypertension. The decrease in NO interferes with smooth muscle vasodilation, resulting in vasoconstriction which plays a role in increasing blood pressure during HD.

In the study by Young *et al.* ADMA levels in patients with stage 3 and 4 CKD were 0.70 ± 0.25 mmol/L [20]. This result is slightly higher than the ADMA levels in our study. We found that in patients with regular HD, ADMA serum level was 0.33 ± 0.22 μM/L. In a study involving 227 CKD patients, the ADMA serum level was 0.46 ± 0.12 μmol /L [21].

A different result was obtained in the study by Raj *et al* [22]. They found that ADMA level in patients with regular HD was 105.3 ± 25.2 μM/L. It was not clear why the ADMA serum level of patients with regular HD in this study was very high.

This study did not prove the existence of a significant relationship between ADMA levels and intradialytic hypertension events. Its influence remained insignificant after adjusted for some antihypertensive agents consumed and changes in Na and Ca levels during HD. Epidemiological studies suggest that there is a link between ADMA levels and hypertension, hypercholesterolemia and diabetes mellitus [23]. Asymmetric dimethylarginine is an endogenous competitive inhibitor of NOS, leading to increased peripheral resistance and increased blood pressure. This study did not prove the existence of a link between ADMA levels and intradialytic hypertension events. A study by Raj *et al.* involving 27 patients with regular HD evaluated the role of NO and ADMA levels on variations in intradialytic blood pressure. They found no significance between NO serum levels and the changes in MAP. ADMA levels did not differ significantly between groups of patients with intradialytic hypotension or hypertension [22].

In our study, ADMA levels were not associated with intradialytic hypertension events this may be caused by the fact that ADMA levels in our study are lower than those in previous studies. The mean ADMA level in this study was 0.33 ± 0.25 μM/L, whereas Raj *et al.* found ADMA levels of 105.3 ± 25.2 μM/L in their patients [22].

The average ET-1 levels pre-HD and post-HD were lower in the intradialytic hypertension group than those in the control group. The increase in serum levels of ET-1 was almost similar in groups with or without intradialytic hypertension. This result was slightly different from that obtained in previous studies. One study found that at the end of HD, the levels of ET-1 in intradialytic hypertension patients were significantly increased compared to the controls [11].

In a study involving 44 patients, ET-1 levels in regular HD patients were higher than those in the control group. Intradialytic hypertension occurred in individuals with a significant increase in ET-1 levels after HD [13]. These results were different from our findings, where ET-1 levels both pre and post-HD in all groups were much lower.

In this research, we did not find a significant association between the levels of ET-1 and intradialytic hypertension events. In a previous study conducted by Chou *et al.,* ET-1 levels obtained pre- and post-HD were higher in the group prone to high blood pressure [11]. Another study found that ET-1 levels decreased significantly in intradialytic hypotension group and increased considerably in the intradialytic hypertension group [22]. Shafei *et al.* found a significant increase in post-HD ET-1 levels in the group of patients with rebound hypertension during HD. It was concluded that changes in ET-1 levels might be involved in the pathogenesis of rebound hypertension and hypotension during HD [13]. This result was in contrast to our study that found no significant relationship between changes in serum levels of ET-1 and intradialytic hypertension events. Again, this might be because our pre-and post- HD ET-1 levels in intradialytic hypertension group were still lower than those in the control group.

This study is the first study to investigate the relationship between UF volume during HD with changing levels of ET-1, NO, and ADMA. In this study, path analysis found a significant association between UF volume and NO levels ($p < 0.01$), while discovering no relationship between UF volume and ADMA as well as ET-1 levels. This finding may explain part of the intradialytic hypertension mechanism through endothelial involvement. This discovery supports the theory that endothelial dysfunction is one of the etiologies of intradialytic hypertension. Currently, no research explains how UF excess can cause a decrease in NO levels.

UF volume during six consecutive HD sessions was larger in intradialytic hypertension group than its counterpart. In general, there is a decrease in blood pressure during ultrafiltration. However, some cases presented with an increase in blood pressure during UF. This study is the first study to investigate the relationship between excessive UF volume and intradialytic hypertension events.

This study revealed that UF and excessive UF volume had a significant effect on the incidence of intradialytic hypertension. In excessive UF, fluid removal from the blood compartment occurs in a significant amount and may lead to sympathetic activation that causes blood pressure increase during HD.

In the study conducted by Kovacik *et al.* that involved 23 patients undergoing regular HD, they found that UF volume correlated strongly with postdialylitic pulse pressure [24]. Currently, there is no study on the relationship between UF volume and intradialytic hypertension events.

To see the causal effect of changes in NO, ET-1 and ADMA levels with toh UF volume, we performed a structural model and analyzed it by using path analysis. Exogenous or independent variables were NO, ADMA and ET-1 levels; while endogenous or dependent variable was intradialytic hypertension. After analysis, we found a significant correlation between UF volume during HD and NO serum levels, between UF volume during HD and intradialytic hypertension, as well as NO serum levels and intradialytic hypertension.

After analyzing the relationship between NO levels and intradialytic hypertension, we found a close correlation between UF volume and NO levels as well as UF volume with intradialytic hypertension. We also found that UF volume during HD had the most powerful of cumulative effect and direct effect on the incidence of intradialytic hypertension.

We also found that the total UF volume had a substantial direct effect on NO serum levels and intradialytic hypertension events. Thus, path analysis concluded the relationship between serum levels of NO, ADMA, ET-1, UF volume and intradialytic hypertension as follows: there was a significant direct relationship between UF volume with intradialytic hypertension events; there was a significant relationship between UF volume during HD with NO serum levels; there was a direct relationship between NO serum levels with intradialytic hypertension events; and there was no direct relationship between UF volume during HD and intradialytic hypertension events through changes in NO serum levels.

Previous research has examined the involvement of endothelium in the pathophysiology of intradialytic hypertension. This study analyzed the endothelial function in patients with intradialytic hypertension and confirmed that endothelial dysfunction occurred in patients with intradialytic hypertension [14].

In our study, we found that one marker of endothelial dysfunction in intradialytic hypertension is NO. Our findings support previous research regarding the involvement of endothelial dysfunction in intradialytic hypertension. This study also found that one of the factors leading to decreased NO is excessive of UF during hemodialysis.

Using path analysis, we can conclude that the pathogenesis of intradialytic hypertension occurs through changes in NO levels and excessive UF volume.

These findings are very useful for patients who are prone to intradialytic hypertension. It will lead to determination of the exact UF volume needed during HD to prevent the occurrence of intradialytic hypertension. It is recommended that patients with fluid overload undergo removal of excess fluid during HD with gradual weight loss in several HD sessions.

CONCLUSION

Excessive ultrafiltration during HD contributes to the incidence of intradialytic hypertension. This is evidenced by the significant relationship between excessive UF and intradialytic hypertension events. The role of excessive UF on intradialytic hypertension incidence is mediated by decreased NO serum levels during HD. This is evidenced by the existence of a direct relationship between NO serum levels and the impact of intradialytic hypertension, as well as indirect relationships between UF volume during HD and intradialytic hypertension events through decreased NO serum levels. Changes in ADMA and ET-1 levels do not play a role in the incidence of intradialytic hypertension. The mean ADMA and ET-1 levels in this study were lower than in previous studies.

Further research should focus on investigating the relationship between intradialytic hypertension and endothelial dysfunction by examining endothelial dysfunction with a more accurate marker. We also need to determine the actual

UF volume necessary to prevent intradialytic hypertension, which can be used by clinicians in handling cases of intradialytic hypertension.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No animals/humans were used for studies that are the basis of this research.

CONSENT FOR PUBLICATION

Consent for publication was obtained.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

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