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ORIGINAL ARTICLE

Pathophysiological, cardiovascular and neuroendocrine changes in hypertensive patients during the hemodialysis session

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The pathophysiological mechanisms of arterial hypertension during hemodialysis (HD) in patients with end-stage renal disease (ESRD) are still poorly understood. The aim of this study is to investigate physiological, cardiovascular and neuroendocrine changes in patients with ESRD and its correlation with changes in blood pressure (BP) during the HD session. The present study included 21 patients with ESRD undergoing chronic HD treatment. Group A (study) consisted of patients who had BP increase and group B (control) consisted of those who had BP reduction during HD session. Echocardiograms were performed during the HD session to evaluate cardiac output (CO) and systemic vascular resistance (SVR). Before and after the HD session, blood samples were collected to measure brain natriuretic peptide (BNP), catecholamines, endothelin-1 (ET-1), nitric oxide (NO), electrolytes, hematocrit, albumin and nitrogen substances. The mean age of the studied patients was 43 ± 4.9 years, and 54.6% were males. SVR significantly increased in group A ($P < 0.001$). There were no differences in the values of BNP, NO, adrenalin, dopamin and noradrenalin, before and after dialysis, between the two groups. The mean value of ET-1, post HD, was 25.9 pg ml^{-1} in group A and 13.3 pg ml^{-1} in group B ($P = < 0.001$). Patients with ESRD showed different hemodynamic patterns during the HD session, with significant BP increase in group A, caused by an increase in SVR possibly due to endothelial dysfunction, evidenced by an increase in serum ET-1 levels.

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INTRODUCTION

The diagnosis of systemic arterial hypertension (SAH) in hemodialysis (HD) patients remains controversial.[1,2] Although it is known that continuous ambulatory monitoring of blood pressure (BP) is a useful measurement for SAH diagnosis, BP measurements before and after HD are frequently used both for the diagnosis and the treatment of SAH. In the HD units, during the dialysis procedure, measurements are routinely made every half hour or, as in most HD centers, every hour, for the purpose of observing the patient's hemodynamic stability during the course of treatment. Unfortunately, these BP measurements have not been used as tools to establish prevention, diagnosis, prognosis and treatment of SAH in dialysis and intradialytic hypertension (IDH). Van Buren *et al.*,[3] in a recent study evaluating the mean interdialytic 44-h systolic ambulatory BP, evidenced that daytime and nocturnal BP were higher among patients with IDH as compared with controls.

Although the pathophysiological mechanisms of IDH are not properly understood, this situation is considered multifactorial. Among the most studied factors are: fluid hypervolemia, sympathetic nervous system (SNS) activity, renin–angiotensin–aldosterone system activity and endothelial dysfunction. The frequency of IDH is estimated at around 10% among patients on HD monitoring. A large-cohort study showed a percentage of 12.2%.[4]

The aim of this study is to evaluate the physiological, cardiovascular and neurohormonal changes and their correlations with BP alterations during HD in patients with chronic renal failure and associated hypertension.

PATIENTS AND METHODS

Study population

Patients of both sexes, aged from 26 to 68 years with chronic kidney disease associated with hypertension, diagnosed according to the criteria of the Kidney Disease Outcomes Quality Initiative (KDOQI) (chronic kidney disease) International Classification and, according to the criteria of the 7th International Joint National Committee on Hypertension (BP $\geqslant$ 140 mm Hg and diastolic blood pressure (DBP) $\geqslant$ 90 mm Hg),[5] undergoing dialysis at the Walter Cantídio University Hospital, Federal University of Ceará (UFC-HUWC), Fortaleza city, Ceará, Brazil, were included in the study. From October 2007 to February 2008, 38 patients were selected, who had BP measured during HD through an automated monitoring device (GE Dinamap Pro 100 (GE Healthcare/GE do Brasil, Sao Paulo, Brazil), Blood Pressure Machine 2000 (Amersham, Bucks, UK)). Subsequently, 17 patients were excluded. The definitive study was carried out with 21 patients in the period from March to July 2008.

Exclusion criteria were diabetes mellitus, chronic pulmonary insufficiency, severe heart failure and stroke. Thus, 21 patients comprised the final sample population in whom the study was performed. Of the 21 patients, 10 had BP increase during HD and thus constituted group A,

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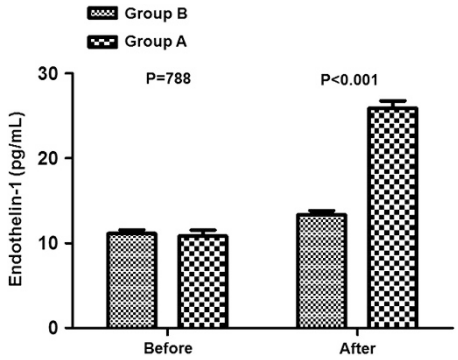

Figure 1. Selection procedure of patients undergoing dialysis selected for the study.

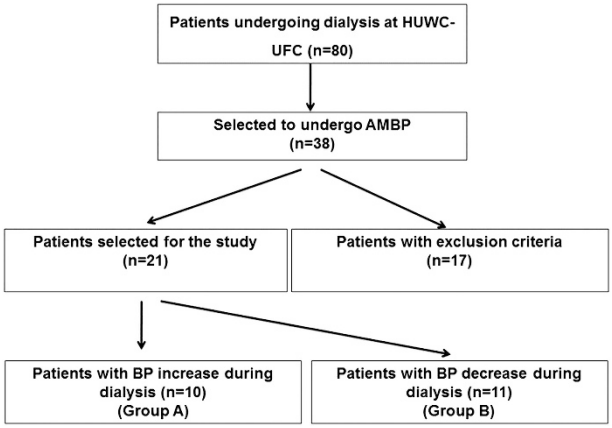

Figure 2. Clinical experiment to investigate intradialytic hypertension in patients undergoing hemodialysis.

whereas 11 patients had BP reduction during dialysis and constituted group B. Figure 1 below summarizes the patient selection procedure used in the study.

Description of the clinical trial day with each patient

Seven days before the date set for the start of the clinical trial, antihypertensive drugs were withdrawn: angiotensin-converting enzyme 2 inhibitors, angiotensin II receptor blockers, beta and alpha blockers and sympatholytic agents. Each selected patient was submitted to a single clinical research experiment. The experiment consisted in undergoing a HD session, with evaluation before, during and after the dialysis procedure, of hemodynamic, cardiovascular and endocrine parameters, mentioned in the objectives of this research. On the day of the clinical trial, prior to the HD, each patient was weighed to calculate body surface and body mass index. Then, the patient was sent to the hospital room used for Holter monitoring. Upon entering the room the patient was asked to sit in the HD chair and rested for 10 min. Then, at 5-min intervals, BP assessments were performed, which were considered the basal values. The cardioscope monitor that measured BP, heart rate (HR) and oxygen saturation during HD was a Dixtal Biomedica—DX20 equipment (Dixtal Biomedica Industria e Comercio LTDA, Sao Paulo, Brazil).

After the first three baseline values were obtained, BP was measured every 15 min, from start to end of the HD session. After the end of the dialysis, BP was verified at 5-min intervals, at three different times. Thus, we performed a total of 23 BP recordings before, during and after the HD session. In parallel, the patient's HR was measured continuously. Oxygen saturation monitoring was maintained throughout the dialytic process.

Soon after, the puncture of the arteriovenous fistula was performed with two number-16 BD needles. At that moment, a pharmacist from the HUWC-UFC central laboratory collected 10 ml of whole blood for the measurement of endothelin-1 (ET-1), nitrites and nitrates and brain natriuretic peptide (BNP) levels. Concomitantly, 10 ml of whole blood were collected in another tube, for the measurement of adrenaline, noradrenaline and dopamine levels. Another 10 ml of whole blood were collected in another tube for the measurement of hematocrit, hemoglobin, urea, creatinine, albumin, alkaline reserve, Na+, K+, Cl−, Mg 2+, Ca++ and ionic calcium. The tubes were then placed in a cooler with ice and transported to the HUWC-UFC Central Laboratory to be centrifuged for 15 min at 3000 r.p.m. at 4–5 °C (refrigerated centrifuge). From one of the 10-ml tubes, serum was separated for biochemical and hematological tests, performed in the same laboratory. Of the two remaining 10-ml samples, one was used for the preparation of 500-microliter aliquots of plasma for the measurement of ET-1, nitrites and nitrates and BNP, whereas the other was used for the preparation of 500-microliter aliquots for the measurement of adrenaline, noradrenaline and dopamine.

The first echocardiogram was performed before the HD and repeated every hour during HD until the end of the dialysis procedure. After individualized heparinization was performed for each patient, the HD procedure was initiated.

Through the echocardiograms, the main anatomic and hemodynamic parameters were recorded, aimed to obtain data from cardiac output (CO) and systemic vascular resistance (SVR) and its association with changes in BP during dialysis. The autonomic nervous system (ANS) activity (SNS, peripheral nervous system) was assessed by recording HR and, consequently, the HR variability (HRV) through Holter, with subsequent spectral analysis of data provided by the HRV in the frequency domain. The study of autonomic nervous system activity was complemented with statistical calculations of HRV assessments to obtain the results in the time domain. A summary of the experiment can be seen in Figure 2.

Table 1. Demographic characteristics of patients with hypertension (group A) and without hypertension (group B) during the hemodialysis session

	Group A		*Group B*		*P-value*
	Mean	*s.d.*	*Mean*	*s.d.*	
Gender					
Male	45.4%	—	80%	—	0.183
Female	54.6%	—	20%	—	
Age (years)	43	4.9	39	3.7	0.503
Body surface area (m^2)	1.6	0.04	1.5	0.06	0.305
Height (cm)	1.6	0.03	1.6	0.03	0.568
Pre-dialysis weight (kg)	58	2.4	55	2.0	0.349
Pre-dialysis body mass index	21.8	0.73	21.3	0.72	0.610
Time in hemodialysis (months)	71	11	72	14	0.931
Ultrafiltration velocity (l)	2.6	0.34	1.2	0.28	0.006

Statistical analysis

When the distributions of two continuous variables were approximately normal, the means of these distributions were compared using the Student's *t*-test. On the other hand, when these distributions were not approximately normal, they were compared using the Wilcoxon Rank Sum test. Proportions were compared using Fisher's exact test. Means, distributions and proportions were considered significantly different when *P*-value was $< 5\%$.

RESULTS

A total of 21 patients were studied, of which 10 had elevated mean arterial pressure (MAP), systolic blood pressure (SBP), DBP, during the course of HD, even after completion of the dialysis procedure (group A). Another group of 11 patients had no increase in MAP, SBP, DBP during the HD, even when new measurements were performed at the end of the HD session (group B).

All patients in both groups studied were non-Caucasian, with a mean age of 39 ± 3.7 years in group A and 43 ± 4.9 years in group B. Group A consisted of 80% males, whereas group B had 54% of females. Mean body weight in group A before HD was 55 ± 2.0 kg and in group B, 58 ± 2.4 kg. Mean time in HD in group A was

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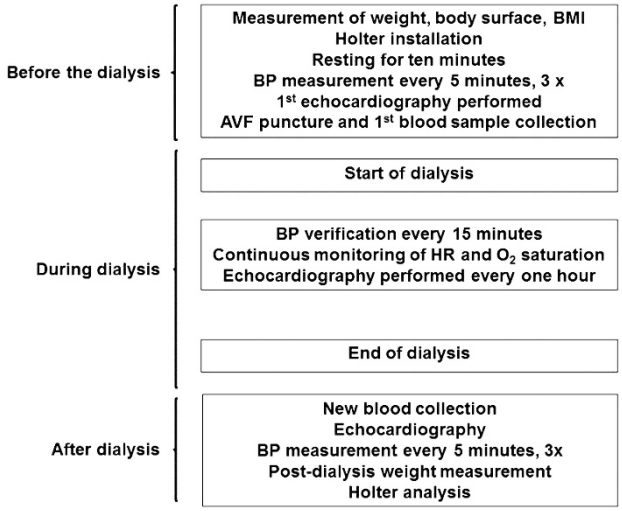

Figure 3. Difference between mean arterial pressure (MAP), before and after hemodialysis in the studied groups.

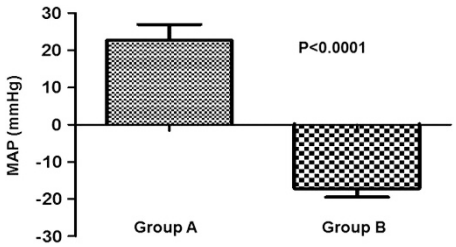

Figure 4. Variation (difference between pre and post-dialysis values) in MAP, SBP and DBP in patients from groups A and B during HD.

72 months and in group B, 71 months. Demographic characteristics of both groups are summarized in Table 1.

Ultrafiltration was assessed through the weight reduction with dialysis, comparing pre- and post-dialysis weight for each patient. Taking into account absolute values, the comparison of weight reduction, pre- and post dialysis, between the two groups showed significant difference: group A = 1.2 ± 0.28 kg vs group B = 2.5 ± 0.34 kg ($P = 0.005$). In relative values (percentage of weight reduction), the comparison between the two groups showed a higher reduction in group B: 4.42 vs 2.18% in group A ($P = 0.007$).

Taking into account the records of MAP absolute values before and after HD, we found that group A showed an increase in mean MAP of +3.3 to +43.6 mm Hg, whereas group B had a decrease in MAP means, ranging from − 3.3 to − 28.7 mm Hg.

When comparing the MAP means in both groups before and after HD, it was observed that group A had an increase in mean MAP values of +21 mm Hg. Group B throughout the HD, and even after dialysis, had a decrease in mean MAP values of − 15 mm Hg, ($P < 0.0001$) (Figure 3). Figure 4 shows the variation in MAP, SBP and DBP in both groups during the HD session.

In group A, the mean HR before the HD was 87 beats min^{-1}. Subsequently, it varied to 86, 85, 91, 89 beats min^{-1} the 1st, 2nd, 3rd and 4th hour, respectively. In group B, the mean HR, pre-dialysis, was 88 beats min^{-1}. It was later modified to 90, 94, 95, 99 beats min^{-1}, during the 1st, 2nd, 3rd and 4th hour, respectively.

Comparing the mean basal values of left ventricular end-diastolic volume with the means obtained after HD, it was verified that during the HD, this echocardiographic parameter showed very similar volume variation, both in groups A and B.

The evolution of the mean systolic ejection fraction during the HD in group A patients varied: 49%, 49%, 47% and 49% in the 1st, 2nd, 3rd and 4th hour, respectively, after an initial value of 48%; in group B, the mean variation of ejection fraction changed, after the initial value of 51%, to 52%, 52% and 53% in the 1st, 2nd and 3rd hour, respectively, for the value of 50% after HD. The comparison of groups through statistical analysis showed that the variable group had $P = 0.518$; the variable time, $P = 0.768$ and variable group × time, $P = 0.768$.

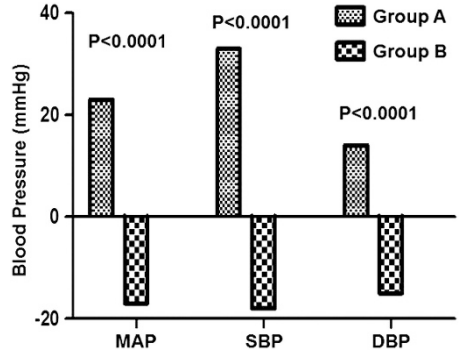

Figure 5. Mean cardiac output (CO) during HD in both groups.

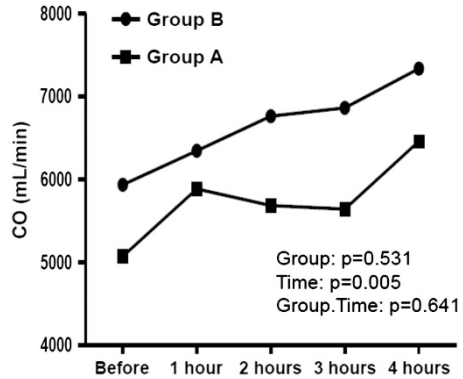

Figure 6. Mean systemic vascular resistance (SVR) during HD in both groups.

The evolution of the mean CO between group A and group B showed the following changes: in group A, comparing the results obtained pre- and post HD, it was observed that there was a mean increase of 1.4 l. The initial value was 5.0 l. The subsequent values in the 1st, 2nd and 3rd hour and right after the 4th hour were 5.8, 5.6, 5.6 and 6.4 l, respectively. In group B, once again using the pre- and post-HD data, it was observed that the increase in the mean CO was also 1.4 l at the end of HD. The initial value was 5.9 l and the posterior values, during the 1st, 2nd, 3rd hour and after the 4th hour, were successively, 6.3, 6.7, 6.8 and 7.3 l, respectively. The use of statistical methods showed $P = 0.531$ for the variable group, $P = 0.005$ for the variable time and $P = 0.645$ for the variable group × time, demonstrating that there were no significant differences in the CO volumes between patients from groups A and B (Figure 5).

The evolution of SVR in patients from group A and group B was 21, 20, 20, 22 and 21 Wood units and 21, 19, 18, 18 and 16 Wood units, respectively (Figure 6).

There was no significant difference regarding the measurements of sodium, potassium, calcium, chloride and albumin before and after HD between the two groups (Tables 2 and 3). There was an increase in alkaline reserve and hematocrit in both groups, an increase in hemoglobin in group B and a decrease in the levels of urea and creatinine in both groups (Table 2).

The values of neurohormones (BNP, nitrates, adrenaline, noradrenaline and dopamine), before and after HD session,

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Table 2. Main laboratory tests pre- and post dialysis from patients in group A (with intradialytic hypertension) and B (without intradialytic hypertension)

	Group A		P-*value*	*Group B*		P-*value*
	Pre HD	*Post HD*		*Pre HD*	*Post HD*	
Sodium (mEq l^{-1})	135	136	0.482	134	135	0.729
Potassium (mEq l^{-1})	4.7	3.2	0.109	5.3	3.5	0.293
Ionic calcium (mEq l^{-1})	1.2	1.4	0.349	1.3	1.4	0.776
Total calcium (mEq l^{-1})	8.9	9.9	0.349	9.2	10.4	0.776
Chloride (mEq l^{-1})	100	97	0.926	100	100	0.920
Alkaline reserve (mEq l^{-1})	17.7	25.7	0.0001	18.2	25.7	0.0001
Urea (mg dl^{-1})	137	38	0.0001	150	46	0.0001
Creatinine (mg dl^{-1})	12	3.7	0.0001	11	3.8	0.0001
Albumin (g dl^{-1})	4.1	4.1	1.0	4.0	4.2	0.64
Hematocrit (%)	33	34	0.03	32	35	0.0001
Hemoglobin (g dl^{-1})	11	11	1.0	10	12	0.0001

Abbreviation: HD, hemodialysis.

Table 3. Differences of laboratory tests pre- and post dialysis from patients in group A (with intradialytic hypertension) and B (without intradialytic hypertension)

	Media	*s.d.*	*95% CI*	P-*value*
Urea				
Group B	−104	8.5	−123 to −85	0.687
Group A	−99	9.5	−121 to −78	
Creatinine				
Group B	−6.8	0.44	−7.73 to −5.78	0.113
Group A	−8.2	0.77	−9.94 to −6.44	
Sodium				
Group B	1	0.45	0.004 to 2.0	0.463
Group A	0.5	0.5	−0.63 to 1.6	
Potassium				
Group B	−1.8	0.1	−2.1 to −1.6	0.124
Group A	−1.5	0.2	−1.9 to −1.0	
Chloride				
Group B	0.04	1.5	−3.29 to 3.37	0.135
Group A	−2.65	0.73	−4.3 to −0.99	
Ionic calcium				
Group B	0.13	0.02	0.08 to 0.18	0.418
Group A	0.16	0.02	0.12 to 0.19	
Total calcium				
Group B	1.2	0.27	0.62 to 1.82	0.612
Group A	1.1	0.17	0.67 to 1.43	
Alkaline reserve				
Group B	7.5	0.55	6.30 to 8.74	0.611
Group A	8.0	0.87	6.07 to 10.01	

Abbreviation: CI, confidence interval.

showed no difference between the two groups (Table 4). In group A, the mean plasma concentration of ET-1 prior to the HD, was 10.8 pg ml^{-1}. In group B, also before starting the HD, the mean plasma concentration of ET-1 was 11.1 pg ml^{-1} ($P = 0.788$). After completion of the HD, the mean plasma concentration in group A increased significantly to 25.9 pg ml^{-1} ($P < 0.001$). In patients from group B, the mean plasma concentration of ET-1 increased slightly to 13.3 pg ml^{-1} (Figure 7). The comparison between hormone levels pre- and post HD in each group (comparing post-HD levels with pre-HD levels) showed significant differences in BNP (group A: −69 vs group B: −338 pg ml^{-1}, $P = 0.0001$), ET-1 (group A: 15.1 vs group B: 2.2 pg ml^{-1}, $P = 0.008$), adrenaline (group A: −128 vs group B: 59 pg ml^{-1}, $P = 0.0001$), noradrenaline (group A: −143 vs group B: −169 pg ml^{-1}, $P = 0.0001$) and dopamine (group A: 0 vs group B: 8 pg ml^{-1}, $P = 0.0001$). There was no difference in nitrate/nitrite levels (group A: 4 vs group B: −4.7 μM, $P = 0.12$).

The comparison of the mean values of serum levels of nitric oxide (NO) and ET-1 of patients in groups A and B, before and after HD, showed that the NO/ET-1 ratio was altered, as a result of the significant increase in ET-1 plasma levels in group A after HD.

DISCUSSION

This is the first study in Brazil and the second in the world to investigate the physiologic, cardiovascular and neurohumoral abnormalities in the complex pathogenesis of hypertension during the HD session.

SAH is a fairly common complication in patients undergoing conventional chronic HD treatment. Approximately 50–90% of chronic HD patients have BP >140/90 mm Hg and only a small minority has adequate BP control.[6] SAH is considered an independent risk factor and has been correlated with morbidity and mortality of patients undergoing HD. Given this evidence, it becomes imperative to maintain rigorous BP control in the hypertensive population of patients on dialysis, considered to be a high-risk one.[7]

A small number of patients experiences progressive and significant increase in BP during HD treatment associated with ultrafiltration.[8] The mechanisms of this paradoxical hypertension remain subject to many interpretations, but it has been speculated that it occurs due to increased plasma volume, renin release and increased activity of the SNS.[9] In the present study, we cannot say that IDH is volume-dependent because patients in group B (without IDH) had higher ultrafiltration volumes, that is, they had higher interdialytic weight gain than patients in group A and did not present hypertension during the HD session. It has been reported that an inappropriate vasoconstriction reflex can occur during HD in response to a reduction in plasma volume, which does not occur during the ultrafiltration alone. This suggests that some vasoconstrictor substances are removed, whereas other vasodilator ones are produced during HD.[10] Another important point to consider is that BNP presented a higher decrease in group B during the HD session, which can be associated to higher

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Table 4. Neurohormones levels pre- and post dialysis from patients in group A (with intradialytic hypertension) and B (without intradialytic hypertension)

	Pre-HD		P-*value*	*Post-HD*		P-*value*
	Group A	*Group B*		*Group A*	*Group B*	
Brain natriuretic peptide (pg ml^{-1})	1643	1720	0.943	1574	1382	0.839
Endothelin-1 (pg ml^{-1})	10.8	11.1	0.788	25.9	13.3	< 0.001
Nitrates/nitrites (μM)	86.3	84.6	0.844	90.3	79.9	0.294
Adrenaline (pg ml^{-1})	208	153	0.568	80	212	0.205
Noradrenaline (pg ml^{-1})	337	488	0.405	194	319	0.202
Dopamine	76	71	0.619	76	79	0.677

Abbreviation: HD, hemodialysis.

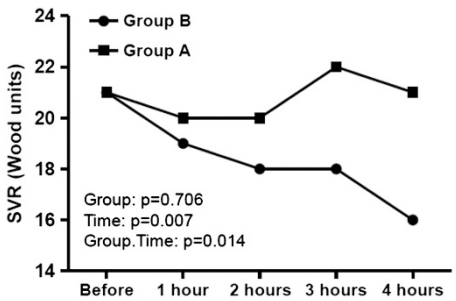

Figure 7. Mean levels of endothelin-1 before and after HD in both groups.

ultrafiltration volumes, and this can explain, at least in part, why this group did not present hypertension during HD.

Regarding the evolution of BP during the 4 h of HD, it was observed that in group A, patients had progressive and sustained elevations in BP, from the 2nd hour of HD until the end. Once the dialysis procedure is finished, new measurements have ratified the elevation in BP when compared with basal ones. In group B (control), patients showed reductions in mean BP during and after HD, when these values were compared with basal ones.

Gunal *et al.*[11] hypothesized that IDH could be caused by increased CO, especially in those patients with large interdialytic weight gain and heart dilation. The authors of this study performed echocardiograms in six patients who had no improvement in SAH with ultrafiltration and concomitant use of antihypertensive medication. Through this additional study, they found improvement in CO from 3.8 to 4.8 l and, in parallel, a change in MAP from 107 to 118 mm Hg, after these patients were submitted to a mean ultrafiltration of 2.5 liters. With continued ultrafiltration, MAP was reduced to 90 mm Hg.

Chou *et al.*,[12] when assessing intradialytic cardiovascular alterations in patients undergoing HD through echocardiograms performed before and after HD, found no significant differences in the evolution of CO between the group with stable BP and the group that showed increased BP during HD.

In our research, echocardiograms assessment, performed hourly during HD sessions, showed that the results of CO evolution in groups A and B constituted a tendency to BP elevation between the start and end of the 4-h HD session. There were no significant differences between the two groups. This hemodynamic behavior was practically the same in both study groups, which suggests that in patients with BP elevation (group A), CO was not the most important physiological finding in BP increase during the 4 h of HD, as a similar increase also occurred in patients who had BP reduction (group B). The only exception was an isolated analysis of the time variable (time: $P = 0.005$). Therefore, we conclude that similarly as with hypervolemia, CO was a relevant component, but not sufficient to explain BP elevation in patients from group A during HD.

During the investigation of hypertension during dialysis (IDH), we verified whether, in addition to CO, the other physiological component of BP—SVR—could be implicated in the increased BP of these patients. There are several mechanisms that can cause elevation of SVR, both functionally and structurally. From the functional point of view, not only the inappropriate activation of the renin–angiotensin–aldosterone system occurs at systemic level, but also the activation, at local level, on the vascular wall itself.[13,14] Other factors involved in the elevation of SVR are: increased activity of the SNS, the elevation of serum endothelin levels and decreased vasodilatation by reduced synthesis of NO.[15] On the other hand, it is known that, from the anatomical viewpoint, another factor that causes increase in SVR is the vascular remodeling by an increase in the arteriolar wall/lumen ratio.[16]

In our study, SVR constituted the predominant physiological finding to explain the behavior of patients in group A, who had elevations in BP during HD, as, in this group, the progressive increase in SVR (measured every hour) accompanied the increase in MAP from start to end of HD. Similarly, in group B patients, SVR decreased in parallel to the decrease in MAP values. This shows that, unlike CO, SVR had a significant role in MAP increase in group A.

Considering, in our research, the relevance of the increase in SVR on the BP increase in patients from group A, we assessed two hypotheses to explain this finding: vascular endothelial dysfunction and SNS hyperactivity.

In relation to the SNS, there have been reports in the medical literature that plasma concentrations of noradrenaline are considered indices of adrenergic activity.[17] Nevertheless, when measured at rest, it is not possible to correlate them with the BP or direct indices of sympathetic function. In the presence of stimuli, such as changes in body position (for example, standing up), we can observe changes in plasma levels of noradrenaline, as well as changes in DBP and heart rate in patients undergoing dialysis.[17]

SVR in patients from group A in our research was the most important hemodynamic parameter that triggered IDH. Considering the possibility that the SNS is responsible for the increase in SVR, we studied, through HRV in the frequency domain (spectral analysis) and time domain (statistical methods), together with the measurements of catecholamines, the diagnostic value of these SNS assessments on this physiological component of BP.

The analysis of the results of mean values of serum electrolytes and hormonal peptides during the baseline period, allow us to infer that the two groups, at this moment of the study, showed similarities in all variables studied. Likewise, after the dialysis procedure, the results of the mean levels of serum concentrations of these hormones and electrolytes, except for ET-1, showed no significant changes from the statistical point of view.

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In our patients, the results of serum catecholamine measurements, measured before and after HD, were not correlated with changes in BP of patients in groups A and B: mean plasma concentrations of adrenaline before and after HD, in patients from group A and group B, did not vary significantly ($P = 0.568$) and ($P = 0.205$), respectively, and showed no correlation with the evolution of BP. In the present study there was a significant variation in the levels of adrenaline and noradrenaline during the HD, with a higher decrease in group A, suggesting that the levels of these hormones do not have a significant role in the genesis of IDH. There was also a significant decrease in BNP during HD, and it was more pronounced in group B, which could be explained by a higher plasmatic volume in this group (these patients presented higher ultrafiltration rates). The higher ultrafiltration rates in group B suggest that increased plasma volume is not an essential factor in the genesis of IDH.

There have been reports of high levels of endothelin in patients with moderate and severe essential hypertension (stage 2 classification of the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7)). As in chronic kidney disease and in patients with secondary hypertension, the endothelins are still the object of research and controversy. As we know, two types of endothelin receptors have been identified (ET-A and ET-B). The ET-A receptor is located predominately in vascular smooth muscle cells, which has the function to mediate the vasoconstriction process and the ET-B receptor is preferentially located in endothelial cells, where it promotes vasodilation through the release of NO and prostacyclin.[18] It is known that endothelins exert multiple actions, including one of singular physiological effect, related to the maintenance of vascular tone.

The importance of endothelins has been demonstrated in animal and human models, through the research of selective antagonists of ET receptors.[19] The blockade of ET-A receptors causes vasodilation, probably due to NO synthesis. In contrast, the blockade of ET-B receptors determines vasoconstriction, indicating that there is a balance between the actions of two receptors.[20]

In our study, the measurement of serum ET-1 levels showed completely different results, when comparing pre- and post-HD. At baseline, the mean values of plasma concentrations of ET-1 showed no differences between groups A and B ($P = 0.788$). However, after HD, analysis of the mean plasma concentrations of ET-1 showed that there had been a significant increase in the group that had an increase in SBP, DBP and MAP, that is, in group A. Patients in group B, which showed a decrease in SBP, DBP and MAP, had no significant increase of serum ET-1. The comparison of the results of plasma levels of ET-1 between the two groups after HD showed statistical significance ($P < 0.0001$), confirming, in our study, the importance of this vasoactive substance in BP increase of patients from group A. The changes in ET-1 levels pre- and post dialysis in each group showed a significantly higher variation in group A, that is, the increment in its levels was higher in group A, suggesting that this higher elevation may have an important role in the genesis of IDH.

It is known that the vascular endothelium releases other vasoactive factors, including NO, causing vasodilation and inhibition of vascular smooth muscle cell proliferation.[21] Experimental models have shown that NO deficiency causes arterial hypertension.[22] Patients in the last stage of chronic kidney disease have a deficiency of NO. Considering this vasoactive hormone as one of the main factors of the complex physiopathogeny of hypertension, it was observed in the abovementioned population group, the triggering of SAH.[23] In the medical literature, there have been publications that refer to the presence of six- to 10-fold higher serum levels of asymmetric dimethylarginine (ADMA) in patients undergoing HD. Although it has been demonstrated that these serum levels decrease in HD lasting 5 h, in a percentage of patients of around 65%, it was observed that, in the interdialytic period, there were further increases.[24]

In summary, the main physiological changes related to the increase of BP during the HD session were caused by an increase in SVR, probably due to endothelial dysfunction, evidenced by ET-1 increase.

Study limitations

Potential limitations of our study stem from the fact that we had included a small number of patients and the fact of being conducted in only one HD center. We had structural and financial problems, so that it was not possible to include a higher number of patients and recruit other centers to participate. It was also not possible to determine the prevalence of IDH in our population. In our study, 10 (47.6%) among 21 studied patients had IDH. The exclusion criteria used (presence of diabetes mellitus, chronic pulmonary insufficiency, severe heart failure and stroke) could have contributed to this high proportion of patients with IDH. We did not study the other patients from this clinic and thus we cannot draw conclusions about the prevalence of IDH in our population. The assessment of the prevalence of IDH was not the objective of the present study, so we think this is not an essential matter to understand the pathophysiological, cardiovascular and neuroendocrine changes during the HD session among those patients with IDH.

What is known about this topic

- The pathophysiological mechanisms of arterial hypertension during hemodialysis in patients with end-stage renal disease are still poorly understood.
- Patients with intradialytic hypertension present higher daytime and nocturnal blood pressure than controls.

What this study adds

- There is an increase in endothelin-1 levels during hemodialysis in patients with intradialytic hypertension.
- Systemic vascular resistance increases during hemodialysis in patients with intradialytic hypertension.
- There is evidence of endothelial dysfunction in the pathogenesis of intradialytic hypertension.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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