

A Single-Centre Experience: Cardiovascular Autonomic Dysfunction in Patients on Long-Term Dialysis

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ABSTRACT

Cardiovascular dysautonomy is a disturbance of the sympathico-vagal balance in the control of the cardiovascular system. The primary objective of this study was to describe the autonomic profile of chronic hemodialysis patients (CHD). This is a cross-sectional observational study, including 22 patients from the hemodialysis (HD) center of the Ibn Sina University Hospital in Rabat. We observed the different cardiac and nephrological characteristics of the patients; Carried out a study of the autonomic nervous system (ANS) by non-invasive methods and established the autonomic profile of the patients. Dysregulation of the cardiovascular autonomic nervous system was found in 72.7% of patients; Vagal disability was the most pronounced autonomic disorder in 63.6%, followed by central (54.6%) and peripheral (50.0%) sympathetic hyperactivity. In multivariate analysis, only the female sex ($p = 0.042$) was an independent risk factor for vagal disability; On the other hand, the HD quality was a protective factor ($r: -0.56, p = 0.021$). Intradialysis hypotension and hypertension appear to be respectively related to decreased baroreceptor sensitivity and sympathetic alpha hyperactivity. The underlying mechanisms of this involvement require further studies before treatment strategies can be developed.

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I. Introduction

Cardiovascular disease is the leading cause of mortality in CHD patients, accounting for 44% of the overall mortality [1, 2]. A number of mechanisms have been proposed to explain this excess mortality, including cardiovascular autonomic dysfunction. Cardiovascular dysautonomy is a disorder of the autonomic nervous system (ANS) which corresponds to the disturbance of the sympathico-vagal balance in the control of the cardiovascular system [3]. Indeed, this condition is one of the main neuro-autonomic complications in CHD; its symptoms are often vague and non-specific. The effects of dialysis and renal transplantation on cardiovascular autonomic dysfunction are covered as well as its significance with regard to dialysis complications, including intra-dialytic hypotension, and cardiovascular mortality. The diagnosis is based on several simple and non-invasive tests evaluating the vegetative control of the cardiovascular system [1]. Early diagnosis of ANS disorders in uremic patients can help prevent serious consequences and apply appropriate therapeutic strategies. The evaluation of autonomic function should be part of the periodic clinical review of uremic patients.

The objective of this study was to describe the autonomic profile of CHD patients, to determine the risk factors involved in autonomic cardiovascular disease and to demonstrate the involvement of these disorders in blood pressure abnormalities during the HD session.

II. Patients and methods:

• Patients

This is an observational cross-sectional study involving 22 patients in the nephrology department of Ibn Sina hospital in Rabat, over 18 years of age, for more than 6 months. Diabetes was the only exclusion criterion.

B. Methods

We carried out a study of the autonomic nervous system at the unit of cardiovascular ANS exploration, in the cardiology department "A" of the Ibn Sina University Hospital in Rabat. In addition, informed, written and signed consent was obtained from each patient before the study began. We observed the different demographic, clinical and paraclinical characteristics of the patients on both cardiac and nephrological levels. We chose Chesterton's definition of intradialytic hypotension, which is a fall of systolic blood pressure (SBP) below 100 mmHg, even asymptomatic or symptomatic of more than 10% of the pre-dialysis SBP during two sessions of HD [4]. Inrig and al define intradialytic hypertension as an increase in BPS ≥ 10 mmHg during HD or immediately after [5].

• Test sequence

Patients were initially placed in a supine position on a tilt table. Basal blood pressure and heart rate (HR) were measured at rest, every 5 minutes for at least 30 minutes and a baseline electrocardiogram (ECG) was performed.

Subsequently the patient underwent the various tests of exploration of the ANS, interspersed with periods of rest. Each autonomic test gives a measurement of the stimulation compared to the basal state. The results are expressed in percentage, whether for sympathetic or parasympathetic stimulations. For sympathetic stimulations related to the measurement of BP variation, only BPS values were analyzed. All calculations consider BPS and HR.

• Deep Breathing test (DB)

Deep Breathing (DB) has a major interest in the determination of vagal response (VR) [6]. The test consists of continuous measurement of HR during six cycles of deep breath in/ breath out, performed for one minute. The respiratory rate has an influence on the RR space at the ECG. The variability of the RR space is studied by electrocardiographic recording throughout the duration of the test at the rate of 25 mm/s, during deep breath in (RR max) and breath out (RR min). A sinus arrhythmia of respiratory origin is physiological, it depends on the vagal activity: it decreases during the stimulation of the pulmonary receptors by the stretch. The result is given as a percentage: (maximum RR - minimum RR / minimum RR) x100. The value is considered normal at 30%, below it is a vagal deficiency and above a vagal overactivity [7].

• Hand Grip test

This is a manual contraction effort used to determine the changes in BP during static stress. It consists in having the patient practice maximum hand pressure with a dynamometer for 15 seconds (isometric contraction) [8].

– *For vagal response:* This test seeks a HR response within 15 seconds of maximum pressure achieved using a dynamometer.

– *For peripheral sympathetic response:* A pressure 50% less than the maximum pressure during 3 minutes makes it possible to evaluate and measure the variation in BP [9]. The response to this test is judged by the measurement of BP or HR variations according to the following formula: BP (or HR) after stimulation - BP (or HR) before stimulation/ BP (or HR) before stimulation. The result is expressed as a percentage. A response equal to 10% is considered normal, above 10% is overactivity, and below 10% vagal or sympathetic disability [9].

• Mental stress

During this test, we ask the patient to do a mental calculation: subtract the number 7 successively from 200 to zero. Some authors have shown that mental calculation would lead to cardiovascular over-reactivity and a change in the baseline values of HR variability [10].

This test induces an increase in central sympathetic activity with decreased blood flow to the extremities and an increase in BP and HR [11].

The central α and β -sympathetic activities are expressed by the changes in BP and HR, respectively, before and after stimulation, according to the following formula: (BP or HR) after stimulation - BP (or HR) before stimulation/ BP (or HR) before stimulation. The result is expressed as a percentage. Usually, a 10% response is considered normal, above 10% is overactivity and less than 10% is known as sympathetic disability.

• Orthostatic test

This is a sympathetic ANS stimulation. Moving from the rest position to the standing position gives rise to a whole series of physiological adaptation processes in normal

population: large volumes of blood are thus displaced. The venous return to the heart is lowered, which causes a fall of the systolic volume and blood pressure by about 40%. The baroreceptors capture these changes and transmit their signals to the cardiovascular center, which responds by stimulating sympathetic tone. Under physiological conditions, the moderate fall in aortic pressure is corrected within 30 seconds by the involvement of baroreflex (BR) arcs, whose starting point is carotid and aortic baroreceptors, inducing an arterial vasoconstriction and tachycardia [12].

C. Statistical analysis

In this study, descriptive statistics include ranks, mean and standard deviation for quantitative variable, frequency and percentage for qualitative variables. The group comparisons were performed by the t-Student test of the independent samples for the quantitative variables and the χ^2 test for the qualitative variables with 95% confidence intervals (CI). Univariate and multivariate logistic regression analyzes were performed to evaluate the association of several independent variables with (the disease under study). These effects were measured by the Odds Ratios (OR) and their 95% CIs on the basis of logistic regression models. The p values were considered statistically significant when they reached values of 0.05 or less. All statistical analyzes were performed using the SPSS program (version 13.0, SPSS Inc, Chicago, IL, USA).

III – Results

A. Patient Characteristics

They are 8 men and 14 women; the average age was 48.45 +/- 8.15 years.

– On the Nephrological level

- The average duration of hemodialysis was 18.59 +/- 5.21 years, with an average Kt/V of 1.45 +/- 0.21 and an average Urea Reduction Percentage (PRU) of 78.50 +/- 3.53, the quality of treatment was optimal in all patients; they were all in euvolemia (clinically, BNP = 157.10 +/- 39.80 ng/l, IVC diameter = 10.02 +/- 2.23 mm).

- Five patients had intradialytic hypertension (22.73%) and four patients had episodes of intradialytic hypotension (18.8%).

- Nutritionally, the mean albumin was 39.10 +/- 1.80 (g/l)
- Patients had no inflammatory syndrome, mean CRP was 5.5 +/- 1.3 mg/l.

– On the Cardiological level

- The baseline HR was 86.7 \pm 5.20 bpm.

- The baseline SPB was 121 +/- 19 mmHg, the diastolic BP was 65.25 +/- 11.51 mmHg.

- All patients were in sinus rhythm.

- In trans-thoracic echocardiography (TTE), 5 patients (22.73%) had left ventricular hypertrophy (LVG) with electrical expression in only two cases (9.1%).

- Left ventricular function was retained in all patients with an average left ventricular ejection fraction (LVEF) of 63.15 \pm 7.33%.

Table 1 summarizes patients' characteristics.

B. Autonomic profile

The dysregulation of the autonomic cardiovascular nervous system was found in 16 patients (72.7%). Figure 1 summarizes the autonomic profile of patients. Deep breathing vagal deficiency (XDB) was the most pronounced autonomic disorder found in 63.6% of patients with an average parasympathetic (vagal) response at 19.34 +/- 3.24% (normal response to 30%).

Table 1. Clinical and demographic characteristics of the patients.

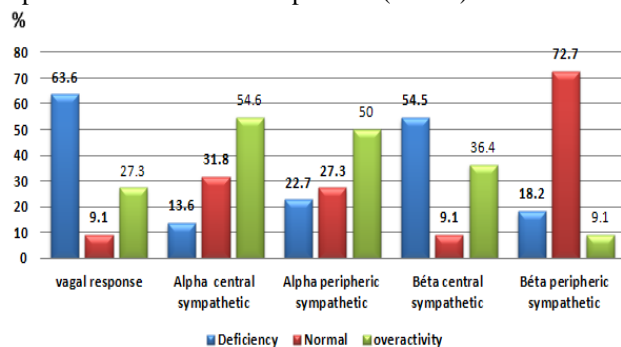
Setting	Values	
Age (Year) *	48,45+/- 8,15	
Sex ratio (H/F)	0,57	
HD duration (Year) *	18,59 +/- 5,21	
Quality of HD	Kt/V	1,45 +/- 0,21
	PRU (%)*	78,50 +/- 3,53
Interdialytic weight gain (IDWG) (g)	2754 +/- 537,25	
BP before test (mmHg)	PAS*	121 +/- 19,23
	PAD*	65,25+/- 11,51
HR before test (bpm)*	86,75+/- 5,20	
per-dialytic incidents	Hypotension **	4 (18,18%)
	Hypertension **	5 (22,73%)
Hemoglobin (g /dl) *	10,54 +/- 0,74	
Albumin (g/l)*	39,10 +/- 1,80	
BNP (ng/l)*	157,10 +/- 39,80	
ECG	RRS	22 (100%)
	HVG	2 (9,1%)
TTE	LVEF (%)*	63,15+/- 7,33
	LVH	5 (22,73%)
	IVC thin and compliant **	22(100%)

* Expressed on average (\pm standard deviation)

** Expressed in numbers (percentage)

Exploration of the sympathetic system essentially found a central alpha hyperactivity in the mental stress test with an average of 20.52 +/- 1.71% in 54.6% of patients and peripheral to the Hand Grip test at 15.65 +/- 2.37% in 50.0% of patients (normal response to 10%).

However, central beta activity was lowered in more than half of the patients (54.5%).The peripheral sympathetic beta response was retained in 16 patients (72.7%).

**Figure 1. Autonomic patient profile.**

In univariate analysis, the female sex ($p = 0.028$), duration of HD ($p = 0.035$) were significant risk factors (RF) predisposing to vagal deficiency in hemodialysis. In multivariate analysis, only the female sex (0.042) constituted an independent RF of vagal deficiency in CHD. (Table 2) The quality of purification was inversely correlated with the occurrence of a vagal deficiency in the Spearman test ($r = -0.56$, $p = 0.021$).

C- Intradialysis incidents

• Intradialysis hypotension

The analysis of the cardiovascular autonomic profile of the 4 patients with intradialysis hypotension demonstrates a decrease in the sensitivity of the baroreceptors in the orthostatic test in 3 patients.

• Intradialysis hypertension

For the five patients with intradialysis hypertension, we found a sympathetic hyperactivity in 4 patients and a vagal insufficiency in 3 patients.

There were no significant differences between patients with and without intradialysis hypertension in terms of biochemical data, cardiac function, dialysis prescription, intradialysis weight loss, or ultrafiltration rate.

III. Discussion

Following the emergence of early studies of uremic autonomic neuropathy performed in small groups of patients and/or using unreliable tests, there has been a proliferation of literature in the past decade. This is mainly due to three reasons: the improvement of dialysis strategies with a continuous increase in life expectancy; the increased interest of clinicians and researchers in autonomic nervous system disorders and the availability of a number of simple, non-invasive tests [3].

In our study, the prevalence of uremic dysautonomia was 72.7%. Cardiovascular autonomic dysfunctions are frequent in uremic patients and can reach 65% in literature [13]. These imbalances are greater in predialysis patients than in dialysis patients. [14].

The mechanisms of these disorders are multifunctional. The decrease in Norepinephrine response to the target organ appears to be a major factor in these anomalies in pre-dialysis patients.

The origin, determinants and consequences of increased sympathetic activation in chronic kidney disease (CRD) have been extensively examined in recent years [15, 16, 17]. Renal ischemia, hypoxia, adenosine and angiotensin II are considered as initial signals [16,17,18]. The significant decrease in sympathetic activity after nephrectomy underlines the role of the CRD as initiators of these alterations [16,17,19]. Another mechanism proposed for increased sympathetic activation suggests that inhibition of nitric oxide (NO) by asymmetric Dimethylarginine, which accumulates in chronic renal failure (CRF), can exert sympathetic excitatory effects in the central nervous system. Afferent sympathetic signaling may be affected by genetic factors and is enhanced by smoking, hypercapnia, hypoxemia, hypercholesterolemia, inflammation, endothelin, angiotensin II, obesity and oxidative stress [20,21].

In this study, parasympathetic deficiency in Deep Breathing was the major autonomic disorder found in 63.6% of patients. These findings are consistent with the literature, and all evaluations of parasympathetic activity (Deep Breathing, Hand Grip, orthostatic test) in pre-dialysis patients were in favor of vagal deficiency. In addition, a significant partial improvement ($p < 0.05$) of the parasympathetic activity was described after hemodialysis [22].

Table 2. Risk factors associated with Parasympathetic disability.

Settings	Univariate analysis			Multivariate analysis		
	OR	IC	p	OR	IC	p
Age (Years)	0.95	[0.59; 1.53]	0.83			
Female sex	1.7	[1.06; 2.81]	0.028	3.25	[1.08; 9.78]	0.042
HD duration (Years)	2.02	[1.42; 8.32]	0.035	0.92	[0.87; 1.13]	0.81
Quality of HD	Kt / V	-0.62	0.025	1.05	[1.01; 1.11]	0.021
	PRU (%)	0.89	0.64			
IDWG (g)	0.97	[0.77; 1.81]	0.66			
Hemoglobin (g/dl)	1.1	[1.52; 2.38]	0.32			

Intradialytic hypotension and autonomic activity

Hypotension is an important intradialytic complication which remains frequent despite advances in hemodialysis technology [23]. Two clinical types of intradialysis hypotension have been reported: asymptomatic progressive decrease in BP with increased HR and a more abrupt decrease in BP with bradycardia and functional symptoms (cramps, nausea and vomiting) [24, 25]. The main causes of hypotension in hemodialysis are: inadequate compensatory mechanisms during ultrafiltration, such as LV dysfunction, inappropriate vascular refilling and a lack of vascular compliance [23,26]. Most of these mechanisms are controlled by the ANS.

During hemodialysis, adequate activation of the sympathetic nervous system is essential for the initiation and maintenance of compensatory mechanisms to maintain BP, in particular an increase in HR and peripheral vasoconstriction; the decrease in blood volume during the hemodialysis session leads, under normal conditions, to a stimulation of the BR that is the cause of the maintenance of the BP by the increase of the HR.

In our study, intradialysis hypotension was observed in 4 patients, 18.18%, of whom 3 had a lower sensitivity of BR (75%). These results are consistent with those of Krepel H and al and Javed F and al, who demonstrated a positive correlation between depression of BR activity and the occurrence of intradialysis hypotension without reactional tachycardia [27, 28].

Sympathetic activation and intradialytic hypertension

Intradialytic hypertension is still underestimated (8-15%), it is a RF in cardiovascular morbidity and mortality [29, 30]. Its pathogenesis is not well understood, probably multifactorial, including subclinical overload, insufficient sodium elimination, activation of the renin-angiotensin system, endothelial dysfunction and/or increased endothelin secretion and modification of the nitric oxide /endothelin balance [31,32]. The activation of the sympathetic nervous system has also been considered as an important factor in its pathogenesis, by an increase in cardiac output and/or peripheral resistances [33].

In our study, 5 patients with intradialytic hypertension were found (22.7%). Sympathetic hyperactivity was diagnosed at Hand Grip in 4 of these patients. According to a study by Rubinger and al, intradialytic hypertension episodes were associated with acute gusts of sympathetic activity with an increase in blood pressure [34].

Therapeutic perspectives: Inhibition of the sympathetic nervous system

Many retrospective studies examined by McQuillan and Chan [35] suggest that α -blockers (clonidine, α -methyl dopamine, Rilmenidine) and β -blockers should be considered as a therapeutic option in the control of BP in CHD patients; in particular Carvedilol and Labetolol in view of their non-dialysable character.

However, the sympatholytic effects of modulators of the renin-angiotensin system remain controversial in patients with CRF and heart failure [36].

Cardiovascular dysautonomy and renal transplantation

Renal transplantation improves most uremic complications. According to Agaewal.A et al, it would also be related to the normalization of all parameters of the ANS activity, as of the third month of post-transplantation [22].

SNA and Erectile Dysfunction

Erectile dysfunction is the most common sexual disorder in CRF. Its prevalence is estimated between 50% and 70% depending on the stage of renal injury [37].

The relationship between abnormal nocturnal penile tumescence (NPT) and autonomic function, as measured by the Valsalva maneuver (parasympathetic impairment), was evaluated in 25 uremic patients and 22 normal subjects. The duration of NTP in uremic patients was lower ($p < 0.01$) than in normal patients. This parameter was significantly correlated with the Valsalva maneuver in uremic patients ($r = 0.62$, $p < 0.01$). There was also a significant correlation ($r = 0.56$, $p < 0.05$) between the Valsalva report and the frequency of sexual intercourse per month in uremic patients with stable and active sexual partners. [38].

These data suggest that ANS dysfunction may be an important factor in the genesis of erectile abnormalities in uremic patients.

IV. Conclusion

In summary, cardiovascular dysautonomy is a frequent complication in uremic patients, and is dominated by parasympathetic insufficiency and sympathetic hyperactivity. In addition, there are signs of deficiency in the sensitivity of cardiac baroreceptors in this population, which is important in the overall integrity of cardiovascular autonomic control.

The underlying mechanisms of this involvement require further studies before treatment strategies can be developed.

VI. Conflicts of Interest

The authors declare that they have no conflicts of interest in relation to this article.

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