



# Differences in Heart Rate Variability Between Diabetic and Non-diabetic Intradialytic Hypotensive Patients

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**Abstract.** The most frequent and troubling side effect in the treatment of hemodialysis is intradialytic hypotension (IDH). This compromises cardiovascular hemodynamics. Heart rate variability (HRV) is a non-invasive measurement of the sympathovagal balance, and provides important information about the autonomic nervous system. Few studies have compared hypotension in diabetic and non-diabetic patients throughout the therapy sessions, with a protocol of intradialytic exercise and high flux hemodialysis/hemodiafiltration therapy. Our work is aimed to evaluate cardiac autonomic regulation during hemodialysis with HRV in hemodynamically unstable patients with chronic renal disease. During a 6-month follow-up of patients, the model suggested that the sympathovagal index (LF/HF) is different between the diabetic from non-diabetic group ( $p < 0.05$ ), and does not necessarily reflect the sympathetic balance. Diabetic patients were differentiated by having lower HRV power components than the non-diabetic group ( $p < 0.05$ ), and during the hypotensive event they showed a sympathetic inhibition, unlike the non-diabetic group that showed a parasympathetic inhibition. It was observed that the compensatory mechanisms were markedly different between two groups studied. This study shows the importance of giving individualized attention and therapies in order to take preventive measures to avoid hypotensive events.

**Keywords:** Hypotension · Heart rate variability · Hemodialysis

## 1 Introduction

Chronic kidney disease is related to the incidence of chronic diseases such as diabetes, obesity and hypertension [1]. Hemodialysis (HD) and Hemodiafiltration (HDF) are the most frequent and well-established treatments [2]. Cardiovascular events are responsible for the majority of deaths and can be attributed to Autonomic Nervous System (ANS) dysfunction. The rapid removal of excess fluid during therapy compromises the cardiovascular hemodynamics. Intradialytic Hypotension (IDH), occurs episodically

with a sudden decrease in arterial pressure. Short-term consequences are symptoms of fatigue, cramps and vomiting. Long-term consequences include permanent damage to the cardiovascular system [3]. The diabetic (DB) population has a predisposition to suffer IDH. It is more difficult for those patients to compensate for ultrafiltration, because they have autonomic or baroreceptor dysfunction [4]. The pathogenesis of hypotension in hemodialysis seems to be multifactorial and is not yet fully understood [5]. Quite a few approaches have been suggested in the literature in order to improve the quality of this therapy [6]. The frequency domain in HRV gives important information about the ANS. The power of the high frequency (HF) signal reflects parasympathetic activity, while the power of low frequency (LF) signal and the sympathovagal (SVI) index of LF to HF (LF/HF) represents the SNA balance [7]. Several studies have showed a reduction in all the spectral indices of sympathetic activity in unstable patients, which precede the decrease in blood pressure, and were interpreted as evidence of deterioration or inhibition of the autonomic response to the elimination of volume [8]. During IDH autonomic changes are characterized by parasympathetic activation and sympathetic withdrawal with bradycardia [9]. Exercise protocols have also been implemented aiming to improve the therapy outcomes. Exercise ensures hemodynamic stability in patients in hemodialysis. In several studies the group with exercise has showed sympathetic predominance, with an increase in the SVI [10]. Other important parameters that have to be controlled are: the use of High-flux HD or HDF, control of dialysate temperature, monitoring of patient parameters, such as HRV, body composition, and nutrition; The systematic use of several of these techniques is necessary in order to provide real-time interventions and improve outcomes [11].

We aimed to evaluate the acute effects of IDH on cardiac autonomic regulation in patients with chronic renal disease with and without Diabetes in a protocol of exercise and High Flux HD/HDF therapy. Its early prediction and prevention will dramatically improve the quality of life and survival for patients with end stage renal disease.

## 2 Materials and Methods

The methodology that we have proposed is based on the one established by the National Institute of Cardiology's HD/HDF clinic in Mexico City, and enhanced by several other innovations:

- 1: Use of intradialytic exercise during the entire dialysis session, through the use of stationary cycling.
- 2: Recording and analysis of HRV and Blood Pressure (BP). Data was acquired during 10 min at three moments: Just at the start of therapy (Time 1), 1.5 h after the session was started (Time 2), and just after the end of the session (Time 3).
- 3: Dialytic Parameters: Blood flow rates were between 400 & 500 ml/min. Dialyzer flow rate was 500 ml/min. Dialysate temperature was 35.5 °C. Linear rate of ultrafiltration. Dialysate composition was: 138 mEq/lit Na<sup>+</sup>, 2 mEq/lit K<sup>+</sup>, 2 mEq/lit Ca<sup>2+</sup>/Nipro Elisio 2.1 Filter; Fresenius Medical Care 4008 H machine.

Twenty-three patients were studied during a six-month interval. They all gave their informed consent. After 471 sessions, there were 101 sessions with hypotensive events,

and this is the data that was analyzed. Patients have the same conditions, except Group 1 is diabetics and Group 2 is non-diabetics.

HRV Analysis: The RR intervals were recorded with a HRV system: Meigaoyi, model ECGLAB 3.0, 1000 Hz sampling rate; We analyzed low-frequency (LF = 0.04 a 0.15 Hz) and high-frequency (HF = 0.15 a 0.40 Hz) components and the ISV ratio.

### 3 Results and Discussion

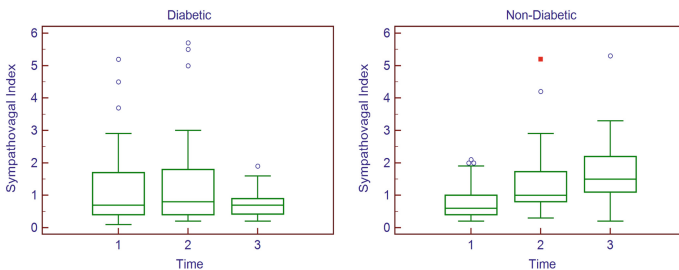
ANOVA for repeated measurements and T student analysis were carried out and post-hoc tests to compare the differences of the HRV and BP.  $P < 0.05$ .

**Table 1.** Blood Pressures Group 1 vs. Group 2 at 3 Times of Therapy.

	DB	NonDB	DB	NonDB	DB	NonDB
Blood pressure	Time 1	Time 1	Time 2	Time 2	Time 3	Time 3
SBP (mmHg)	159 ± 25	163 ± 19	132 ± 31	135 ± 24	105 ± 20*	125 ± 16*
DBP (mmHg)	70 ± 15*	80 ± 24*	66 ± 15*	74 ± 21*	59 ± 11*	67 ± 15*
MBP (mmHg)	100 ± 17*	108 ± 18*	89 ± 20	95 ± 20	75 ± 12*	86 ± 12*
HR (bpm)	71 ± 10*	79 ± 11*	74 ± 14*	82 ± 14*	74 ± 13*	79 ± 15*

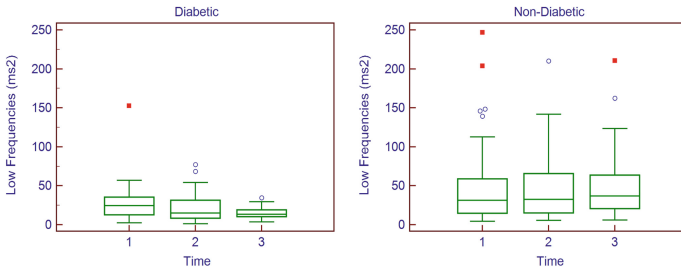
\* $p < 0.05$  Group I vs. Group II

Table 1 shows the values of systolic blood pressure (SBP), diastolic blood pressure (DBP), median blood pressure (MBP) and heart rate (HR) in both groups. The elimination of volume by ultrafiltration (UF) during hemodialysis causes a series of hemodynamic responses. This can be seen in the Blood Pressure in Table 1. Through the therapy in both Groups the blood pressure falls more than 20 mmHg, which causes severe hypotension, it means that the ANS cannot compensate for UF. The decrease is significant greater ( $p < 0.05$ ) in DB patients. It could be explained because Diabetic Patients have been reported to have impaired ANS activity. Heart rate, did not change through the therapy in a significant manner in both groups. But was significant higher ( $p < 0.05$ ) in the non-diabetic group.



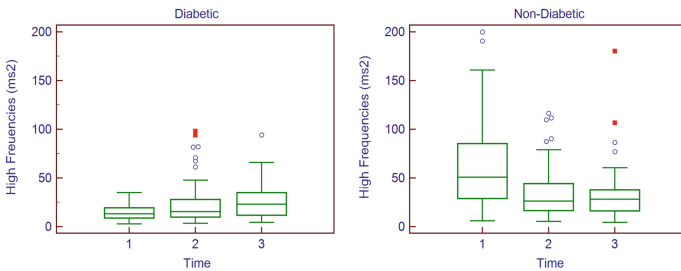
**Fig. 1.** Sympathovagal Index at 3 times during hemodialysis sessions with hypotension in diabetic and non-diabetic patients.

The SVI describes the balance between sympathetic and parasympathetic activity, in Fig. 1. We can observe in the diabetic group, a decrease in the index at the end of the therapy, compared to time 1 and 2 ( $p < 0.05$ ). In the non-diabetic group, there is an increase in the middle and end compared to the beginning ( $p < 0.05$ ).



**Fig. 2.** Low-frequency power ( $ms^2$ , absolute units) at 3 times during hemodialysis sessions with hypotension in diabetic and non-diabetic patients.

In Fig. 2 we can observe that the low-frequency components decrease at time 3 compared with 1 and 2 ( $p < 0.05$ ) with group 1, while it does not change in a statistically significant manner ( $p > 0.05$ ) in all times, with group 2. LF power spectrum was significant lower ( $p < 0.05$ ) in group 1 compared to group 2.



**Fig. 3.** High-frequency power ( $ms^2$ , absolute units) at 3 times during hemodialysis sessions with hypotension in diabetic and non-diabetic patients.

Figure 3 shows the increase of high-frequency components at the end of session, compared to time 1 and 2 ( $p < 0.05$ ) in Group I. A decrease is shown at the middle of the session compared to time 1 and 3 ( $p < 0.05$ ) for group 2. HF power spectrum was significant lower ( $p < 0.05$ ) in group 1 compared to group 2.

The data found in group 1 agrees with previous studies where they are as described in the literature in a hypotensive event, where there is a decrease in the SVI due to a decrease in the LF power (sympathetic activity), and an increase in the HF power (parasympathetic activity). But unlike previous studies that showed a bradycardic activity, in our study the heart rate did not change, this can be due to the intradialytic exercise that the patients perform, and keeps the heart rate active.

On the other hand, in the data found in group 2 the SVI increases, but it is not due to a sympathetic increase, because we observe that the LF power does not change significantly, but the HF power decreases significantly at the end of the therapy, and this is the power that is influencing the sympathovagal balance. This discovery found in group 2, suggests a parasympathetic withdrawal, and can be thought of as a last line of defense when the sympathetic system alone cannot deal with the cardiovascular control at the end of the HD session and it is due to the parasympathetic system's effort to maintain the blood pressure appropriately. Finally, the finding that LF does not decay through the therapy can be a result of the dialytic exercise, that keeps the sympathetic activity from decreasing.

## 4 Conclusion

The measurement of the ANS activity with HRV represents a simple and non-invasive method, important in the determination of the balance of autonomic modulation in patients with renal insufficiency. Which is during a short-term protocol, significant differences were found intra-dialysis between diabetic and non-diabetic patients. The occurrence of IDH events, depends on the pathology of the patient.

For both groups, SNA changes are presented at the middle and end of the therapy. We suggest this is an important period of time to measure the patient. As the ISV is a ratio, an increase is not necessarily due to sympathetic activation, we suggest that the role of the frequency components is more important. Although the use of exercise did not prevent the event of hypotension to happen, in our study we can observe a positive effect in non-diabetic group, which can indicate that it helps the ANS to compensate for UF in the therapy.

The ANS is only part of the monitoring for the individualized therapy that must be done in order to improve the quality of the treatment. We are currently undertaking preliminary studies evaluating the use of a multifrequency body composition analyzer that provides information about the patient's body composition and hydration status. Real time HRV analysis through the use of ECG Holter. Long term protocols of exercise to evaluate which is the most appropriate that help to reduce adverse events. Also, we are carrying out preliminary metabolic analyses at the start and end times of HD/HDF treatment in some patients, to provide information that indicates the advisability of providing supplementary nutrition. We foresee that the integration of all these parameters into a personalized therapy that will increase longevity and quality of life for patients under renal replacement therapy.

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**Conflict of Interest Statement.** The authors declare that they have no conflict of interest.

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