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High Sensitivity Cardiac Troponin I, a Possible Biomarker of Diastolic Dysfunction in Asymptomatic Patients in Hemodialysis

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Abstract

Objective: There are clinical conditions with histological evidence of non-ischemic myocardial necrosis that are associated with elevated troponin levels, such as the structural and functional alterations of the Left Ventricle (LV) that occur in Left Ventricular Diastolic Dysfunction (LVDD). We analyzed the relationship between the ultrasensitive Troponin I biomarker (TnI-US) and LVDD in a cohort of asymptomatic Hemodialysis (HD) patients.

Methods: Descriptive cross-sectional study including 80 patients. Categorical variables were compared using Chi2 test, and quantitative variables were compared with Student's t-test or Mann-Whitney U-test. ROC curve to determine the predictive value of TnI-US levels for LVDD. Logistic regression analysis to determine the factors independently associated with LVDD.

Results: The mean TnI-US was 31.2 ± 59.3 pg/ml, and 40% of patients had TnI-US >20 pg/ml. These patients had higher frequency of LVDD (56.3% *vs.* 25%, p=0.005). 37.5% of patients had LVDD and higher proportion of moderate/severe Left Ventricular Hypertrophy (LVH) (63.3% *vs.* 36.7%, p=0.02), lower heart rate at the start of HD (66.9 ± 8.6 bpm *vs.* 77.2 ± 43.6 bpm, p=0.03), and higher TnI-US (47.4 ± 81.9 pg/ml *vs.* 21.5 ± 38.1 pg/ml, p=0.005). Logistic regression analysis showed that TnI-US >20 pg/ml [OR: 4.1 (95% CI 1.3-12.1), p=0.01] and moderate/severe LVH [OR: 5.1 (95% CI 1.7-15.2), p=0.003] were independently associated with LVDD, while an increase in heart rate [OR: 0.9 (95% CI 0.8-0.9); p=0.02] was independently associated with a lower risk of LVDD.

Conclusion: TnI-US can be used as a biomarker for LVDD in asymptomatic patients on HD.

Keywords: Ultrasensitive troponin I • Diastolic dysfunction • Chronic kidney disease • Hemodialysis

Introduction

Patients with End-Stage Renal Disease (ESRD) undergoing Hemodialysis (HD) have an elevated risk of developing Cardiovascular Disease (CVD). CVD complications represent the leading cause of death, occurring in more than 50% of cases [1]. Left Ventricular Diastolic Dysfunction (LVDD) is defined as impaired ventricular relaxation resulting in reduced ventricular filling. It is a common finding in these patients, with prevalences of 50-65%, and may appear in very early stages, even in the absence of clear clinical symptoms, [2] and is associated with increased mortality [3]. LVDD is mainly associated with Left Ventricular Hypertrophy (LVH). LVH appears early in ESRD as a result of pressure and volume overload, accompanied by myocardial fibrosis and impaired relaxation, which together with the CVD risk factors present in HD patients are the protagonists involved in LVDD [4]. In addition, inherent factors of ESRD such as volume overload, anemia, or high-output fistulas [5,6] also contribute.

The clinical consequence of LVDD is that these patients have a low threshold for developing heart failure. Moreover, when these patients are subjected to ultrafiltration during HD, they may experience a rapid drop in left ventricular pressure, increasing the risk of sudden hypotension and hemodynamic instability [7]. Early detection of LVDD could lead to identifying those patients at higher risk of events and to early intervention and treatment [2,8]. Therefore, it is essential to explore useful serum biomarkers in the early evaluation of LVDD in these patients.

Troponins are structural proteins of the myocardium, belonging to the contractile system of cardiomyocytes and involved in cardiac contraction. When the integrity of the myocardial cell membrane is damaged, troponins are released into circulation, inducing a rapid and transient elevation of these proteins in the blood [2,8]. Two different types can be quantified, Troponin I (TnI) and Troponin T (TnT). TnT was the first to be isolated using non-isotopic immunoassay techniques, while more recently, methods for the detection of TnI have been developed. Due to their high tissue specificity, troponin determination is used in the detection of myocardial damage in different contexts, with high sensitivity and specificity for the detection of myocardial injury. In recent years, the appearance of ultrasensitive methods has allowed the detection of very small concentrations of this biomarker in blood, as well as better precision in its quantification, which has enhanced its use in contexts other than ischemic heart disease [9,10].

Cardiac troponin release indicates myocardial damage, but the cause is not always acute coronary syndrome. Clinical conditions exist with histological evidence of non-ischemic myocardial necrosis associated with troponin

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elevation, such as structural and functional abnormalities of the LV in response to pressure and volume overload [7,11]. Elevation of cardiac troponins in the presence of structural and functional abnormalities of the LV has been mentioned in several studies [8,12-14]. These enzymes can be elevated in asymptomatic HD patients, with TnT concentrations exceeding the 99th percentile of the healthy population in up to 95% of cases [2,8,15,16], while TnI is elevated in 15-30% of cases [13,15-17]. There are studies that find a relationship between TnT and LVDD [2,18-21], but data on the association between LVDD and Ultrasensitive troponin I (TnI-US) in patients with ESRD are limited.

The objective of this study was to analyze the relationship between the TnI-US biomarker and LVDD in a cohort of asymptomatic patients on HD in our center.

Materials and Methods

Patients

A descriptive cross-sectional study was conducted, which included all patients with ESRD on HD in the Nephrology Department of the Hospital General Universitario de Ciudad Real. The inclusion criteria were: a time on HD of more than 3 months, receiving at least three HD sessions per week, and having had a recent echocardiogram within the last year. The exclusion criteria were: class III or IV heart failure according to the New York Heart Association (NYHA), presence of a known primary cardiomyopathy, severe valvular disease, myocardial infarction in the last six months, unstable angina, presence of infectious signs, underlying malignancy, major surgery in the previous month, or refusal to give consent.

Clinical data

The following variables were collected: age, gender, height, weight, Body Mass Index (BMI), etiology of ESRD, time on HD, data on associated comorbidity such as arterial hypertension, Diabetes Mellitus (DM), or dyslipidemia, and history of ischemic heart disease. The data were obtained from the patient's medical history through our center's computer program. Analytical determinations were performed before the HD session and after the long interdialytic period. These included values of serum hemoglobin, calcium, phosphorus, Parathyroid Hormone (PTH), albumin, cholesterol, LDH, CPK, and TnI-US, with a TnI-US value >20 pg/ml being considered pathological, corresponding to the upper limit of the 99th percentile of normal values with the immunoassay used in our institution (Beckman Coulter, USA). Vital signs such as systolic blood pressure, diastolic blood pressure, and heart rate were collected before the start of the dialysis session, on the same day as the analytical extraction. Patient data was included in a dissociated database designed to preserve the anonymity of the participants.

Ecocardiographic parameters

The diagnosis of LVDD was established by the presence of at least two of the following parameters: E (mitral inflow E wave) / E' (mitral annular tissue Doppler E' wave) ratio >15; E' wave velocity <7 cm/s; left atrial volume index >34 ml/m^2; and tricuspid regurgitation velocity >2.8 m/s [22]. LVH was defined as moderate if interventricular septum thickness was >14 mm and severe if >16 mm [23]. Finally, Left Ventricular Ejection Fraction (LVEF) was considered normal if it was greater than or equal to 50% [23].

Statistical analysis

Categorical variables were expressed as percentages and compared using the Chi2 test. Quantitative variables were expressed as mean ± standard deviation and compared using Student's t-test or the Mann-Whitney U test depending on whether the data followed a normal distribution or not. Normality of each variable was assessed using the Kolmogorov-Smirnov test. We performed a sensitivity analysis with ROC curve to determine the predictive value of TnI-US for LVDD. Using logistic regression analysis, we determined the variables that were independently associated with the presence of LVDD. Statistical significance was established at p<0.05 and Confidence Intervals (CI) were estimated with a 95% confidence level. The statistical program used was SPSS 25.0.

Results

The study included 80 patients from the HD unit of our hospital. The mean age was 67 ± 13 years, and 57.5% of patients were male. The most frequent etiology of ESRD was diabetic nephropathy, followed by glomerular pathology. Among the CV risk factors, the most frequent was arterial hypertension (86%), followed by dyslipidemia (75%), DM (52%), and overweight (51%). 32.5% of patients had a previous diagnosis of ischemic heart disease. In the echocardiogram findings, 41% had moderate/severe LVH, and 37.5% had LVDD. Only 8.8% of patients had pathological LVEF (Table 1).

The mean TnI-US was 31.2 ± 59.3 pg/ml, and 40% of patients had TnI-US values >20 pg/ml. We compared patients with TnI-US >20 pg/ml *vs*. 20 pg/ml. We decided on this value because in the sensitivity analysis of TnI-US as a predictor of LVDD, we obtained a cutoff value, determined by the J or Youden index, of 21.3 pg/ml (sensitivity 60%, specificity 74%) (Figure 1). With these results, we decided to maintain the cutoff value >20 pg/ml, as it is the reference value used in our laboratory under usual conditions, as mentioned previously.

Patients with TnI-US levels >20 pg/ml were older (70 ± 10 years *vs*. 65 ± 14 years, p=0.05), had higher systolic blood pressure at the beginning of HD (137.5 ± 16.4 mmHg *vs*. 125.5 ± 21.1 mmHg, p=0.008), and were more anemic with lower hemoglobin levels (10.8 ± 1.5 g/dl *vs*. 11.5 ± 1.3 g/dl, p=0.02). Cardiologically, there was a higher percentage of patients with LVEF <50% (21.9% *vs*. 0%, p=0.001) and LVDD (56.3% *vs*. 25%, p=0.005). No differences were found in the rest of the parameters analyzed, including the previous diagnosis of ischemic heart disease (Table 2).

37.5% of patients had LVDD and were older (71 ± 10 years *vs*. 65 ± 14 years, p=0.04), had a higher percentage of arterial hypertension (96.7% *vs*. 3.3%, p=0.03), higher systolic blood pressure at the start of HD (139 ± 17 mmHg *vs*. 125 ± 20 mmHg, p=0.02), a higher proportion of moderate/severe LVH (63.3% *vs*. 36.7%, p=0.02), lower heart rate at the start of HD (66.9 ± 8.6 bpm *vs*. 77.2 ± 43.6 bpm, p=0.03), and higher TnI-US (47.4 ± 81.9 pg/ml *vs*. 21.5 ± 38.1 pg/ml, p=0.005) (Table 3).

The logistic regression analysis showed that TnI levels >20 pg/ml [OR: 4.1 (95% CI 1.3-12.1); p=0.01] and the presence of moderate/severe LVH [OR: 5.1

Table 1. Baseline characteristics.

Characteristics	Age (years)	67 ± 13
	Men/women	57.5%/42.5%
	BMI (Kg/m^2)	25.7 ± 5.6
	Time in HD (years)	5.2 ± 5.3
	Arterial Hypertension	86.3%
	DM	52.5%
	Dyslipidemia	75%
	Overweight	51.2%
	Ischemic heart disease	32.5%
	Moderate/severe LVH	41.3%
	LVEF <50%	8.8%
	LVDD	37.5%
Primary Renal Disease	Diabetic nephropathy	32.5%
	Glomerular Disease	20%
	Nephroangiosclerosis	17.5%
	Chronic Tubulointerstitial Nephritis	10%
	Other causes	20%

Quantitative data are expressed as mean ± standard deviation, categorical data are expressed as percentages.

Abbreviations: BMI: Body Mass Index; HD: Hemodialysis; DM: Diabetes Mellitus; LVH: Left Ventricular Hypertrophy; LVEF: Left Ventricular Ejection Fraction; LVDD: Left Ventricular Diastolic Dysfunction

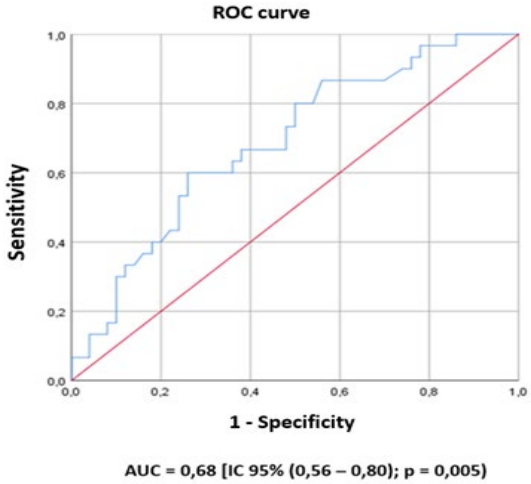

Figure 1. ROC curve sensitivity analysis of TnI-US value predictor of LVDD.

Table 2. Patient characteristics according to ultrasensitive troponin I levels.

		TnI-US ≤ 20 pg/ml (60%)	TnI-US>20 pg/ml (40%)	p value
Baseline Characteristics	Age (years)	65 ± 14	70 ± 10	0.05
	Male	50%	68.8%	0.09
	Time in HD (years)	5.8 ± 6.2	4.2 ± 3.6	0.13
Comorbidities	Arterial hypertension	83.3%	90.6%	0.35
	DM	50%	56.3%	0.58
	Dyslipidemia	72.9%	78.1%	0.59
	Overweight	56.3%	43.8%	0.27
	Ischemic heart disease	27.1%	40.6%	0.20
Measurement of vital signs at the beginning of HD	Systolic blood pressure (mmHg)	125.5 ± 21.1	137.5 ± 16.4	0.008
	Diastolic blood pressure (mmHg)	65.4 ± 12.8	70.4 ± 11.3	0.08
	Heart rate (bpm)	68.4 ± 11.3	70.5 ± 10.3	0.51
Laboratory Parameters	Hb (g/dl)	11.5 ± 1.3	10.8 ± 1.5	10.8 ± 1.5
	Calcium (mg/dl)	8.6 ± 0.6	8.8 ± 0.6	8.8 ± 0.6
	Phosphorus (mg/dl)	4.7 ± 1.5	4.6 ± 1.3	4.6 ± 1.3
	PTH (ng/ml)	426 ± 428.5	429.5 ± 508.4	429.5 ± 508.4
	Albumin (g/dl)	3.7 ± 0.3	3.6 ± 0.4	3.6 ± 0.4
	HDL (mg/dl)	40.4 ± 13.7	49.5 ± 22.2	49.5 ± 22.2
	LDL (mg/dl)	65.1 ± 27.3	71.1 ± 21.4	71.1 ± 21.4
	CPK (mg/dl)	53.3 ± 42.4	76.8 ± 63.8	76.8 ± 63.8
	LDH (mg/dl)	210.8 ± 126.3	245.5 ± 124.3	245.5 ± 124.3
	CRP (mg/dl)	2.1 ± 3.7	2.2 ± 3.3	2.2 ± 3.3
Echocardiographic Parameters	Moderate/severe LVH	35.4%	50%	0.19
	LVEF <50%	0%	21.9%	0.001
	LVDD	25%	56.3%	0.005

Quantitative data are expressed as mean ± standard deviation, categorical data are expressed as percentages.
Abbreviations: TnI-US: Ultrasenstive troponin I; HD: Hemodialysis; DM: Diabetes Mellitus; Hb Hemoglobin; PTH: Parathormone; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; CPK: Creatine-Phosphokinase; LDH: Lactate Dehydrogenase; CRP: C Reactive Protein; LVH: Left Ventricular Hypertrophy; LVEF: Left Ventricular Ejection Fraction; LVDD: Left Ventricular Diastolic Dysfunction.

(95% CI 1.7-15.2); p=0.003] were independently associated with the presence of LVDD, while an increase in heart rate [OR: 0.9 (95% CI 0.8-0.9); p=0.02] was independently associated with a lower risk of LVDD (Table 4).

Discussion

In our study, we analyzed the relationship between serum TnI-US levels and LVDD in asymptomatic HD patients in our unit. The echocardiography data showed that 41% had moderate/severe LVH, 37.5% had LVDD, and only 8.8% had a pathological LVEF. Echocardiography is one of the most useful techniques for detecting asymptomatic cardiac pathology. LVH is at the forefront of echocardiographic abnormalities in HD patients. However, LVDD has been gaining increasing importance in recent years. In our sample, 41% had moderate/severe LVH, which is lower than the prevalence of LVH >70% reported in the literature for HD [3,12,24]. The difference is probably due to the fact that we did not consider patients with mild LVH, thus underestimating the real prevalence of LVH in our unit. LVH represents a mechanism of adaptation of the cardiac muscle to sustained excess work due to pressure or volume overload, and HD treatment is a situation where a greater number of predisposing factors for its development coincide. The clinical consequences are mainly systolic and diastolic dysfunction, with the development of congestive heart failure, ischemic heart disease, arrhythmias, and hypotension during HD [4,25-27].

The LVDD has been poorly studied to date and data is highly variable,

Table 3. Factors associated with left ventricular diastolic dysfunction.

		LVDD (37.5%)	Not LVDD (62.5%)	p value
-	Age (years)	71 ± 10	65 ± 14	0.04
	Male	60%	40%	0.72
Comorbidities	Arterial hypertension	96.7%	3.3%	0.03
	DM	56.7%	43.4%	0.56
	dyslipidemia	80%	20%	0.42
	Overweight	50%	50%	0.86
	Ischemic heart disease	43.3%	56.7%	0.10
Measurement of vital signs at the beginning of HD	Systolic blood pressure (mmHg)	139 ± 17	125 ± 20.2	0.02
	Diastolic blood pressure (mmHg)	68.4 ± 13.4	66.8 ± 11.9	0.59
	Heart rate (bpm)	66.9 ± 8.6	77.2 ± 43.6	0.03
Laboratory Parameters	TnI-US (pg/ml)	47.4 ± 81.9	21.5 ± 38.1	0.005
	Hb (g/dl)	11 ± 1.4	11.3 ± 1.4	0.46
	Calcium (mg/dl)	8.6 ± 0.6	8.7 ± 0.6	0.77
	Phosphorus (mg/dl)	4.7 ± 1.4	4.7 ± 1.5	0.83
	PTH (ng/ml)	326.1 ± 273.6	488.1 ± 534.2	0.20
	Albumin (g/dl)	3.6 ± 0.3	3.7 ± 0.3	0.32
	HDL (mg/dl)	45.8 ± 19.3	43 ± 17.3	0.72
	LDL (mg/dl)	70 ± 25.3	66.1 ± 25.2	0.50
	CPK (mg/dl)	76.5 ± 68.3	54.4 ± 39.6	0.36
	LDH (mg/dl)	238.6 ± 129.1	216.4 ± 124.5	0.59
	CRP (mg/dl)	2.4 ± 4.3	2 ± 2.9	1
Echocardiographic Parameters	LVEF <50%	10%	90%	0.75
	Moderate/severe LVH	63.3%	36.7%	0.02

Quantitative data are expressed as mean ± standard deviation, categorical data are expressed as percentages.
Abbreviations: DM: Diabetes Mellitus; HD: Hemodialysis; TnI-US: Ultrasenstive troponin I; Hb: Hemoglobin; PTH: Parathormone; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; CPK: Creatine-Phosphokinase; LDH: Lactate Dehydrogenase; CRP: C Reactive Protein; LVH: Left Ventricular Hypertrophy; LVEF: Left Ventricular Ejection Fraction.

Table 4. Risk factors for left ventricular diastolic dysfunction.

	OR	CI 95%	p value
TnI-US>20 pg/ml	4.1	1.3-12.1	0.01
Moderate/severe LVH	5.1	1.7-15.2	0.003
Heart rate (bpm)	0.9	0.8-0.9	0.02

Abbreviations: TnI-US: Ultrasenstive troponin I; LVH: Left Ventricular Hypertrophy; OR: Odds Ratio; CI: Confidence Interval.

perhaps related to the difficulty in its definition. It is estimated that between 50% and 65% of patients with advanced CKD or on HD suffer from it. This percentage is higher compared to the 37.5% in our sample, although literature suggests that it may be overestimated by pseudonormalization of the E/A ratio produced by excessive preload [4,28,29]. Furthermore, the number of patients with depressed LVEF was only 8.8% compared to the 15-30% reported by other authors [28]. These echocardiographic findings could be justified by the lower prevalence of LVH in our patients.

The mean TnI-US was 31.2 ± 59.3 pg/ml, and 40% of the patients had TnI-US values >20 pg/ml. In our study, when analyzing the sensitivity of TnI-US as a predictor of LVDD, we obtained a cutoff value determined by the J or Youden index of 21.3 pg/ml (sensitivity 60%, specificity 74%). Based on these results, we decided to establish the cutoff value >20 pg/ml, as the reference value used in our laboratory under usual conditions, which coincides with other studies [15]. In patients with ESRD, TnI rises in 15-30% of cases [13,15-16]. The percentage increases when high-sensitivity techniques are employed, as seen in the study by Kumar N, et al. [17], where they found an elevation of TnI-US in 41%, which is in agreement with our findings. The mechanism by which TnI levels are elevated in asymptomatic HD patients is unclear. It has been shown that a decrease in glomerular filtration rate does not lead to an increase in troponin values, and even an improvement in renal function after kidney transplantation does not result in a decrease in TnI values [30]. It has been suggested that it may be related to the HD procedure, which can cause microvascular damage, subendocardial hypoperfusion, changes in cell membrane permeability, and ultimately myocardial damage [31].

Patients with TnI-US levels >20 pg/ml had older age, higher systolic blood pressure at the start of HD, and lower hemoglobin levels. No relationship was observed between elevated TnI-US levels and a history of ischemic heart disease, indicating that it is not only a marker of ischemic heart disease. Luño J, et al. [1], found similar results, concluding that factors such as age, arterial hypertension, or anemia, in addition to acute coronary syndrome, can increase troponin levels in these patients.

Regarding LVDD, patients with higher systolic blood pressure at the start of HD, older age, and arterial hypertension are at greater risk. The most common conditions associated with LVDD are aging, arterial hypertension, and comorbidities of CKD. All of these are associated with the development of myocardial fibrosis and decreased ventricular distensibility, leading to LVDD [4]. These factors related to CKD itself support that CKD per se is a cardiovascular risk factor and that these patients have an increased risk of suffering an event [32].

After adjusting for significant variables from the univariate analysis, the factors that independently associate with the development of LVDD are moderate/severe LVH, TnI-US levels >20 pg/ml, and heart rate. The association between LVDD and LVH in HD is widely demonstrated in the literature. Different authors in their works, such as Pecoits-Filho R, et al. [4] or Bardají A and Martínez-Vea A [7], affirm that LVDD is the consequence of myocardial changes, such as myocardial fibrosis and altered relaxation, which occur in HD patients with LVH.

On the other hand, the mechanism that justifies the elevation of troponins in patients with LVDD is not entirely clear, although we know that they can be released in situations of non-ischemic myocardial injury [7]. There is greater

evidence of the relationship between TnT and LVDD as shown in different publications [2,18,21]; however, the association between TnI and LVDD has been less studied. Otsuka K, et al. [10], analyzed the relationship between serum levels of TnI and LVDD in HD, establishing as a possible underlying mechanism an alteration at the level of the coronary microcirculation and diastolic pressure overload in the LV. Buiten MS, et al. [13], concludes that TnI appears to be superior to TnT as a marker of LV dysfunction in asymptomatic patients on HD [33-35].

Our study has several limitations. Firstly, those inherent to the observational design, which prevent the assessment of potential confounding factors not included in the analysis. Secondly, the sample size is relatively small. Therefore, it is necessary to contrast these results with studies with a larger sample size and with bias control elements. Despite these limitations, we conclude that TnI-US may be a biomarker strongly associated with LVDD in asymptomatic HD patients. Further studies with a larger number of patients would increase the evidence of this claim, in order to carry out early intervention and treatment.

Conclusion

Finally, in our study, the increase in heart rate was independently associated with a lower risk of LVDD. In the literature, we find evidence that excessive control of heart rate can be one of the mechanisms involved in producing LVDD. Wahlberg K, et al. found that a higher heart rate can have important hemodynamic benefits in patients with LVDD. This author conducted a study with patients with LVDD with pacemakers and found that increasing heart rate above 80 beats per minute significantly improved quality of life and functional capacity. According to Esfandiari S, et al. Increased heart rate allows shortening of early LV relaxation and produces better cardiac performance. These findings suggest that lower heart rates result in slower relaxation, the LV takes longer to fill resulting in higher filling pressures with greater cellular stress on myocardial tissue and ultimately LVDD.

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