

Original Paper

# What Is the Meaning of Increased Myocardial Injury Enzymes during Hemodialysis? A Tissue Doppler Imaging Study

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## Key Words

Hemodialysis · Myocardial damage · Tissue Doppler imaging

## Abstract

**Background:** Cardiovascular death is decreasing in the general population; however, it appears in still higher rates and even increases gradually in hemodialysis (HD) patients. This situation has led to a debate about cardiovascular adverse effects of HD which lead to significant changes in cardiac and hemodynamic events. It is known that troponins are often elevated in HD patients, and high levels of troponin are associated with increased mortality. Therefore, it is difficult to interpret the value of elevations in chronic kidney disease patients.

**Methods:** Echocardiographic and biochemical parameters of 41 patients treated with HD were evaluated before and after a HD session. **Results:** HD led to an increased heart rate, and tissue Doppler imaging parameters such as early diastolic mitral peak velocity (E)/early diastolic myocardial peak velocity (é) and septal é decreased significantly after HD. HD caused an increase in troponin I, myoglobin and cardiac creatine kinase (CK MB) levels ( $p = 0.019$ ,  $p < 0.001$  and  $p = 0.018$ , respectively). A decrease in the left ventricular peak systolic myocardial (LV S') velocity ( $p = 0.011$ ) was detected in patients with increased levels of cardiac damage markers (group 2) compared to those without increased levels of cardiac damage markers (group 1) in HD. **Conclusion:** A decrease in LV S' velocity was found to be an independent predictor of an increase of myocardial injury enzymes in HD (odds ratio = 1.099;  $p = 0.039$ ). We concluded that HD may lead to significant acute stress upon the myocardium.

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## Introduction

Cardiovascular disease (CVD) is 10–20 times more common in chronic kidney disease (CKD) patients than in the general population [1]. The incidence of CVD in hemodialysis (HD) patients is 40%, with an annual rate of mortality of 9%, and it accounts for approximately 50% of deaths [2]. An increased risk of CVD in CKD patients cannot be fully explained with the classical risk factors. Besides the traditional risk factors such as hypertension, diabetes mellitus, hyperlipidemia, smoking and physical inactivity, the risk is further increased due to CKD-specific risk factors such as oxidative stress, inflammation, increased vascular calcification, hypoalbuminemia, proteinuria, hyperhomocysteinemia, microinflammation, high level of parathyroid hormone, myocardial calcification and anemia [1–4].

Although HD is a life-saving treatment method, it has serious complications such as hypotension (20–30%), muscle cramps (5–20%), nausea and vomiting (5–15%), headache (5%), chest pain (2–5%), back pain (2–5%), pruritus (5%), shivering and fever (<1%) [5]. The HD process leads to significant cardiac and systemic hemodynamic changes. Serious complications increasing the mortality and morbidity may occur due to intradialytic hypotension (IDH) such as myocardial ischemia, arrhythmia, transient ischemic attack, syncope, mesenteric ischemia, ischemic optic nerve atrophy and volume overload following an insufficient dialysis resulting from incomplete dialysis. IDH has been shown to be an independent risk factor for HD patients [6].

Although deaths from CVD have decreased in the last decade and despite the advances in HD and medication technology, cardiovascular mortality remains at high levels and it even increases in HD patients. Thus, questions concerning the adverse cardiovascular effects of HD have been raised. The pathophysiology of these adverse effects is an important new field of study for nephrology because there is more and more evidence suggesting that subclinical myocardial ischemia is induced by HD and that this is a common phenomenon. HD patients are susceptible to myocardial ischemia due to the hemodynamic changes occurring during HD [7, 8]. Silent ST segment depression is seen between 15 and 45% in this patient group [9, 10]. However, the concept of ischemia induced by HD (without atherosclerotic plaque rupture) has received little attention. It has been demonstrated that significant new regional wall motion abnormalities occur during and after HD. This is a response to the ischemia during physiological or pharmacological stress [11–13]. These data support the evidence that HD can induce subclinical ischemia. Considering that this condition is repeated 3 times a week with HD, it can be said that subclinical ischemia, together with continuous but reversible abnormalities in the regional function of the myocardium, may lead to cardiac failure. The rate of cardiovascular and all-cause mortality in patients who have undergone renal transplantation is lower than in patients on HD, which supports this prediction [14, 15].

On the other hand, a contribution of primary coronary artery disease to the occurrence of HD-related ischemia remains uncertain. In the conducted studies, there was no correlation between the development of intradialytic ST depression and angiographically confirmed coronary artery disease [16]. This also indicates that obstructive coronary artery disease out of the main coronary arteries may lead to myocardial hypoperfusion. Likewise, coronary flow depends not only on high vascular patency, but also on the degree of microvascular disease. Probably, HD patients have a specific microvascular disease because of the high prevalence of diabetes, hypertension and vascular calcification [17].

It is known that troponins are often elevated in HD patients, and high levels of troponin are associated with increased mortality [18, 19]. Although at first there was a debate on the origin of elevated troponin, it has become clear that troponins have a cardiac origin [20]. Creatinine kinase and cardiac creatine kinase (CK MB) are less elevated in HD patients compared to troponins [21]. Some studies demonstrated that the levels of CK MB predict

mortality risk, although the long-term prognostic value of these elevations in creatine kinase (CK) has yet to be proven [21, 22]. Myoglobin concentration is associated with creatinine clearance [23]. Therefore, it is difficult to interpret a possible elevation in CKD patients. This is not specific to the heart, and because there is a large amount of myoglobin in the skeletal muscles, its contribution to the diagnosis of acute myocardial infarction (AMI) is limited. Brain natriuretic peptide (BNP) is a natural RAAS antagonist; its release is increased proportionally with ventricular dilation and pressure load [24, 25]. In vitro stabilities of BNP and N-terminal prohormone of BNP (NT-proBNP), an inactive metabolite, are suitable for routine clinical use. BNP is superior to the other neurohormones in the determination of diagnosis and prognosis in left ventricular failure and in the subacute phase after AMI [26, 27]. It has an excellent negative predictive value in high-risk patients [28]. In the conducted studies, NT-proBNP was shown to be an independent parameter in the prediction of prognosis both in the short and long term [28, 29].

The objective of this study was to evaluate and investigate the acute effects on the cardiovascular system that may be produced by HD, which has a vital importance for end stage renal disease (ESRD) patients. Evidence that HD may induce myocardial ischemia, and intradialytic systolic and diastolic myocardial function changes, was detected with conventional, pulsed-wave Doppler and tissue Doppler echocardiography modalities; blood pressure changes were identified with ambulatory blood pressure monitoring (ABPM); blood samples were collected to evaluate acute changes in the markers of cardiac damage and electrolyte changes, and changes in cardiac rhythm were detected by Holter electrocardiography.

## Material and Methods

### *Study Design and Patients*

Forty-one patients receiving HD therapy for at least the last 3 months because of ESRD that had developed due to any reason were included in the study. The study protocol was approved by the Human Ethics Committee of Cumhuriyet University Research Hospital School of Medicine and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants before their enrollment.

### *Inclusion Criteria*

HD patients with ESRD aged  $\geq 18$  years who received HD 3 times a week for at least 3 months were included. Informed consent was obtained from all patients.

### *Exclusion Criteria*

Exclusion criteria were malignant disease, an uncontrolled psychiatric disorder, patients with a poor general condition and paralytic patients, pregnancy, patients with alcohol abuse, drug and substance addiction, and patients with bundle branch block and arrhythmias.

### *Patient Evaluation*

A detailed medical history and findings of the physical examination of all patients were recorded. Holter monitors for heart rhythm evaluation and, synchronically, ABPM were installed 15 min before the HD session. The monitoring was continued during HD and following HD (total 24 h). Echocardiography was performed at baseline before HD and control echocardiography was carried out at the end of a 4-hour HD session. Blood samples were collected before HD and collected again at the end of a 4-hour HD session to evaluate the changes in markers of cardiac damage and electrolyte levels. Routinely performed procedures and previous therapies received by the patients were continued during HD.

### *Echocardiographic Evaluation*

Following a resting period of 15 min, all the patients underwent two-dimensional and Doppler echocardiographic evaluation, including tissue Doppler imaging (TDI) with the echocardiogram device (Vivid 7, GE Healthcare, USA) using a 3.5-MHz transducer before and after HD. Echocardiograms of all patients were

recorded as standard parasternal and apical images with the patients lying in the left lateral position. The measurement and recordings were carried out as normal inspiratory and end-expiratory. Doppler records of M-mode, pulse and continuous waves were obtained for each case. All the measurements were performed based on the standards of the American Society of Echocardiography by the same cardiologist. Left atrium volumes were measured in two planes with modified Simpson's method. Left atrial diameter (LAD), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), stroke volume, left atrial volume (LAV), cardiac output, ejection fraction (EF), mitral annular plane systolic excursion (MAPSE) and tricuspid annular plane systolic excursion (TAPSE) values were defined from the recordings obtained with the conventional echocardiography. In the pulsed-wave echocardiographic transmittal flow screenings, early diastolic mitral peak velocity (E), late diastolic mitral peak velocity (A), isovolumic relaxation time (IVRT), deceleration time (DT) and transmittal flow propagation velocity (Vp) were measured based on the reference images of the apical 4 chamber. On TDI, left ventricular peak systolic myocardial velocity (LV S'), left ventricular peak systolic myocardial velocity (RV S'), early diastolic myocardial peak velocity ( $\epsilon$ ) and late diastolic myocardial peak velocity ( $\acute{a}$ ) were recorded with apical 4-chamber images using a sampling volume of 5 mm in the septal and lateral mitral and tricuspid annular regions. All Doppler measurements were carried out manually. E/A, E/ $\epsilon$  and E/Vp rates, E/ $\epsilon$  [30] as a parameter of left ventricular filling pressure and pulmonary capillary wedge pressure (PCWP) using the formula  $1.9 + 1.24 (E/\epsilon)$  were calculated from the data obtained in a study by Nagueh et al. [31].

#### Statistical Analysis

Statistical analyses were evaluated using SPSS (Statistical Package for Social Sciences) 18 for Windows software. Mean, standard deviation, maximum and minimum values were calculated as the descriptive statistics. Paired samples t test,  $\chi^2$  test, Mann-Whitney U test, Pearson's correlation analysis and logistic regression analysis were used for evaluation of the data in the independent groups. The data were expressed as the means  $\pm$  standard deviation, number of subjects and percentages. Values of  $p < 0.05$  were considered statistically significant.

## Results

Forty-one patients (19 females, 22 males) with a mean age of  $54.7 \pm 15.4$  years who had received HD therapy 3 times a week for a mean of  $56.8 \pm 62.3$  months because of ESRD that had developed due to any reason were included in the study. Demographic, clinic, etiological causes and laboratory outcomes of the patients are outlined in table 1. When hemodynamic parameters before and after HD were compared, no statistically significant difference was found in systolic blood pressure, diastolic blood pressure, mean arterial pressure and pulse pressure ( $p = 0.093$ ,  $p = 0.229$ ,  $p = 0.123$  and  $p = 0.113$ , respectively; table 2; fig. 1), while a significant increase was observed in heart rate ( $p < 0.001$ ) and a significant decrease in PCWP ( $p < 0.001$ ; table 2; fig. 2).

#### Conventional Echocardiographic Parameters

When conventional parameters of the cases before and after HD were compared, a statistically significant decrease was found in LVEDD and LVESD ( $p < 0.001$  and  $p < 0.001$ , respectively), while there was a significant increase in EF, cardiac output and MAPSE parameters ( $p < 0.001$ ,  $p = 0.012$  and  $p = 0.012$ , respectively). A significant decrease was found in LAV after HD ( $p = 0.01$ ). No significant difference was found in LAD, stroke volume and TAPSE parameters between both periods ( $p = 0.160$ ,  $p = 0.586$  and  $p = 0.442$ , respectively; table 2; fig. 3a).

#### Pulsed-Wave Doppler Echocardiographic Parameters

When pulsed-wave Doppler echocardiographic parameters before and after HD were compared, a significant decrease was found in E, E/A and E/Vp parameters after HD ( $p < 0.001$ ), while there was a significant increase in DT ( $p = 0.037$ ). No significant difference was found in A, IVRT and Vp parameters between both periods (table 2; fig. 3b).

**Table 1.** Demographic and clinical features of the patients in the study

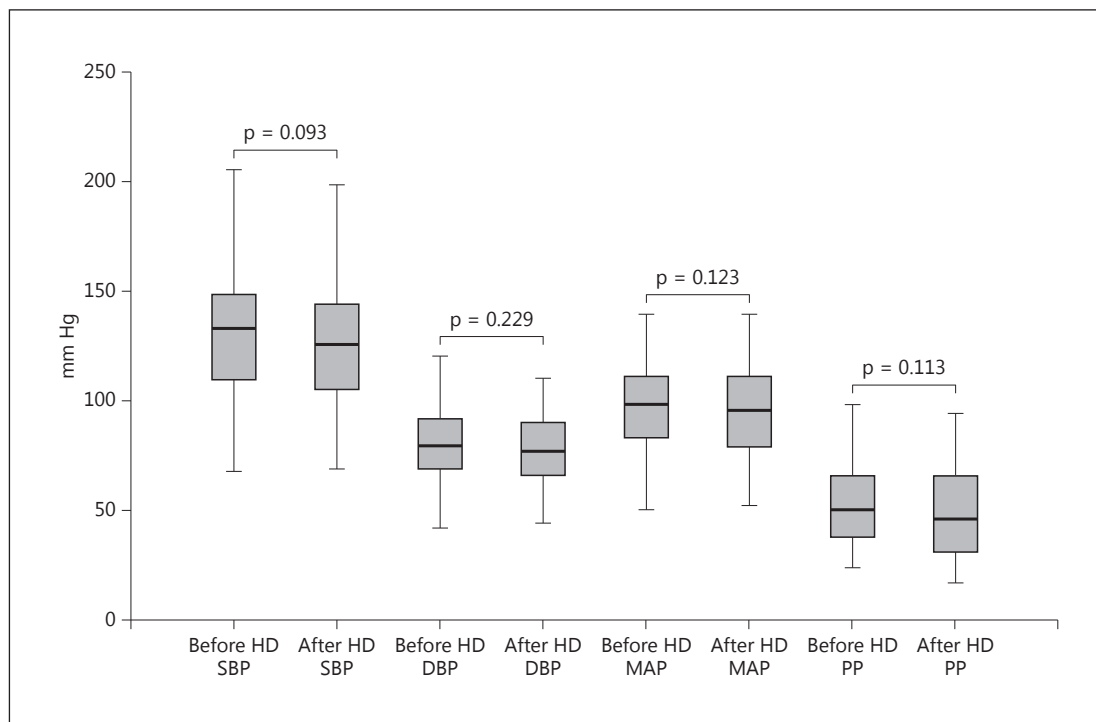
Age, years	54.7 ± 15.4
Gender, female/male, n (%)	19 (46.3)/22 (53.7)
Height, cm	158 ± 13
Weight, kg	62 ± 15
Body mass index	25.7 ± 6
Body surface area, m <sup>2</sup>	1.62 ± 0.2
Systolic blood pressure, mm Hg	134 ± 32
Diastolic blood pressure, mm Hg	81 ± 16
Mean arterial pressure, mm Hg	99 ± 20
Pulse pressure, mm Hg	54 ± 22
HD duration, months	56.8 ± 62.3
Vascular access, AVF/catheter, n (%)	36 (87.8)/5 (12.2)
Excess weight, kg	1.98 ± 0.9
Patients with residual urine, n (%)	18 (43.9)
Residual urine, ml	360 ± 589
Amount of ultrafiltration, ml	2,347 ± 98
Diabetes mellitus, n (%)	16 (39)
Hypertension, n (%)	16 (39)
Coronary artery disease, n (%)	5 (12.2)
Smoking, n (%)	4 (9.7)
Drug use, n (%)	
ACEi or ARB	16 (39)
β-Blockers	11 (26.8)
CCB (nondihydropyridine group)	15 (36.6)
Phosphate binders	35 (85.4)
Vitamin D analogues	13 (31.7)
Erythropoietin	16 (39)
Statins	7 (17)
Etiological cause of ESRD, n (%)	
Diabetes mellitus	16 (39)
Hypertension	8 (19.5)
Glomerulonephritis	4 (9.76)
Chronic pyelonephritis	2 (4.88)
Obstructive uropathy	1 (2.44)
Amyloidosis	2 (4.88)
Polycystic kidney disease	4 (9.76)
Unknown	4 (9.76)
Biochemical parameters	
Kt/V	1.48 ± 0.3
URR, %	70 ± 0.8
Albumin, g/dl	3.1 ± 0.5
Cholesterol, mg/dl	173 ± 63
Triglyceride, mg/dl	182 ± 139
LDL cholesterol, mg/dl	94 ± 41
HDL cholesterol, mg/dl	32 ± 15
C-reactive protein, mg/l	11.3 ± 16.6
Hemoglobin, g/dl	11.2 ± 1.2
Parathormone, pg/ml	233.3 ± 161.9

Data are expressed as means ± standard deviation and numbers with percentages in parentheses. ACEi = Angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; AVF = arteriovenous fistula; CCB = calcium channel blockers; HDL = high-density lipoprotein; LDL = low-density lipoprotein; URR = urea reduction rate.

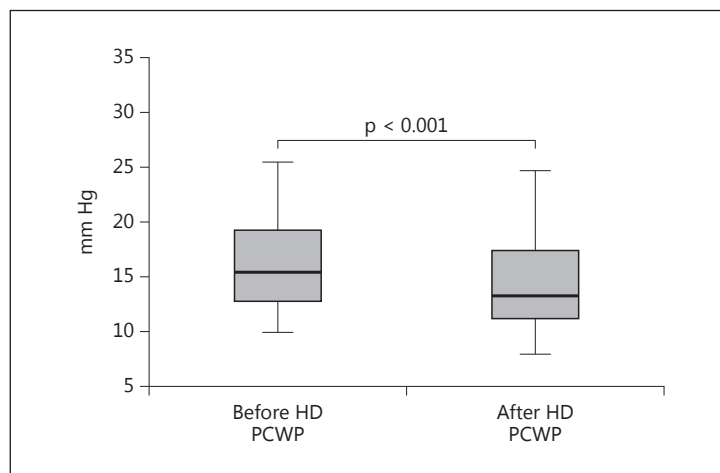
**Table 2.** Effect of HD on hemodynamic conventional Doppler and tissue Doppler echocardiographic and biochemical parameters

Variable	Before HD	After HD	p*
<b>Hemodynamic parameters</b>			
Systolic blood pressure, mm Hg	134±32	128±32	0.093
Diastolic blood pressure, mm Hg	81±16	78±17	0.229
Mean arterial pressure, mm Hg	99±20	95±21	0.123
Pulse pressure, mm Hg	54±22	49±22	0.113
Heart rate, beats/min	77±13	84±17	<b>&lt;0.001</b>
PCWP, mm Hg	17±6	15±5	<b>&lt;0.001</b>
<b>Conventional echocardiographic parameters</b>			
Stroke volume, cm <sup>3</sup> /m <sup>2</sup>	49.8±14.9	50.6±15.2	0.586
EF, %	56.1±7.2	60.2±6.4	<b>&lt;0.001</b>
Cardiac output, l/m <sup>2</sup>	3.8±1.3	4.2±1.3	<b>0.012</b>
LAD, cm	5.2±6.4	3.8±0.7	0.160
LAV, cm <sup>3</sup> /m <sup>2</sup>	5.1±1.5	4.7±1.4	<b>0.010</b>
LVEDD, cm	4.6±0.6	4.3±0.5	<b>&lt;0.001</b>
LVESD, cm	3.5±0.6	3.1±0.5	<b>&lt;0.001</b>
MAPSE, mm	1.5±0.2	1.6±0.2	<b>0.012</b>
TAPSE, mm	2.2±0.3	2.2±2.2	0.442
<b>Pulsed-wave Doppler echocardiographic parameters</b>			
A, cm/s	86.3±27.1	84.3±22.3	0.266
E, cm/s	85.5±22.3	66.9±23.0	<b>&lt;0.001</b>
E/A	1.0±0.5	0.8±0.4	<b>&lt;0.001</b>
E/Vp	2.1±0.7	1.6±0.7	<b>&lt;0.001</b>
DT, ms	196.9±53.5	220.1±60.9	<b>0.037</b>
IVRT, ms	110.2±31.6	123.3±38.1	0.054
Vp, cm/s	40.4±6.8	43.8±10.8	0.064
<b>Tissue Doppler echocardiographic parameters</b>			
Lateral á, cm/s	8.9±2.9	9.2±3.1	0.549
Lateral é, cm/s	8.8±3.3	8.1±2.9	0.104
Septal á, cm/s	7.2±1.9	7.4±2	0.474
Septal é, cm/s	6.4±2	5.8±1.9	<b>0.042</b>
E/é	12.2±4.6	10.3±3.9	<b>&lt;0.001</b>
LV S' velocity, cm/s	7.3±1.6	7.7±1.9	0.139
RV S' velocity, cm/s	12±2.8	12±2.7	0.471
<b>Biochemical parameters</b>			
BUN, mg/dl	69±23	23±10	<b>&lt;0.001</b>
Creatinine, mg/dl	8±3.2	3.4±1.8	<b>&lt;0.001</b>
Sodium, mM	136±2.8	136±2.7	0.633
Potassium, mM	5±1.0	3.5±0.6	<b>&lt;0.001</b>
Calcium, mg/dl	8.3±0.7	9.6±0.8	<b>&lt;0.001</b>
Magnesium, mg/dl	3±0.5	3.3±0.4	<b>&lt;0.001</b>
Phosphate, mg/dl	5.1±2.1	2.9±1	<b>&lt;0.001</b>
Bicarbonate, mM	18.5±4.6	24.9±5.1	<b>&lt;0.001</b>
Blood glucose, mg/dl	124±53	104±30	<b>0.027</b>
<b>Cardiac damage indicators</b>			
CK, U/l	61.7±30.8	65.2±35.7	0.175
CK MB, U/l	8.5±2.3	9.5±2.7	<b>0.018</b>
Myoglobin, ng/ml	112±49.4	138.8±72.1	<b>&lt;0.001</b>
NT-proBNP, fmol/ml	216.2±141.7	209.7±119	0.327
Troponin I, ng/ml	0.03±0.1	0.31±0.7	<b>0.019</b>

Data are expressed as means ± standard deviation. Bold values indicate statistical significance. \* Paired samples t test.



**Fig. 1.** Effect of HD on hemodynamic parameters. DBP = Diastolic blood pressure; MAP = mean arterial pressure; PP = pulse pressure; SBP = systolic blood pressure.

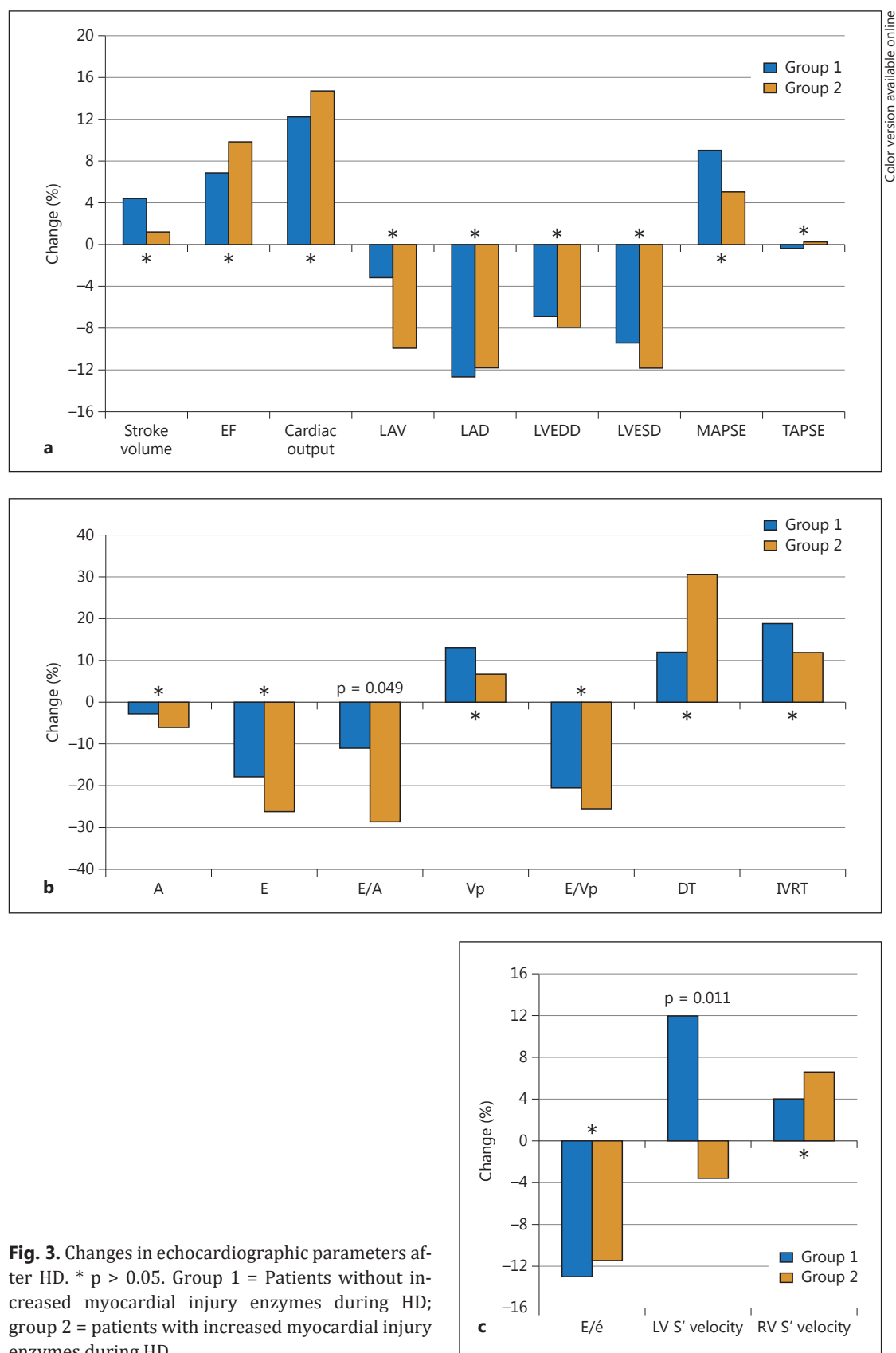


**Fig. 2.** Effect of HD on PCWP.

### Tissue Doppler Echocardiographic Parameters

When TDI diastolic function parameters before and after HD were compared, a significant decrease was found in  $E/e'$  and septal  $e'$  parameters ( $p < 0.001$  and  $p = 0.042$ , respectively), while no significant difference was observed in lateral  $a'$ , lateral  $e'$  and septal  $a'$  parameters between both periods. There was no significant difference found in LV  $S'$  velocity and RV  $S'$  velocity parameters before and after HD sessions (table 2; fig. 3c).





**Fig. 3.** Changes in echocardiographic parameters after HD. \*  $p < 0.05$ . Group 1 = Patients without increased myocardial injury enzymes during HD; group 2 = patients with increased myocardial injury enzymes during HD.



**Table 3.** Demographic and clinical features of the groups with and without increased myocardial injury enzymes

Variable	Group 1 (n = 27)	Group 2 (n = 14)	p
Age, years	52.2±14.7	59.6±16.1	0.115 <sup>a</sup>
Gender, female/male, n (%)	13 (48.1)/14 (51.9)	6 (42.9)/8 (57.1)	0.504 <sup>b</sup>
Height, cm	158±14	157±12	0.694 <sup>a</sup>
Dry weight, kg	60.2±14	65.2±17	0.376 <sup>a</sup>
Body mass index	23.9±4.4	26.6±7.8	0.559 <sup>a</sup>
Residual urine, ml	389±643	304±486	0.839 <sup>a</sup>
Excess fluid, ml	1,850±1,005.7	2,243±790	0.307 <sup>a</sup>
Body surface area, m <sup>2</sup>	1.61±0.2	1.64±0.2	0.654 <sup>a</sup>
HD duration, months	50.9±62.4	68.1±62.8	0.204 <sup>a</sup>
Amount of ultrafiltration, ml	2,209±1,032	2,614±807	0.391 <sup>a</sup>
Vascular access, AVF/catheter, n (%)	24 (88.9)/3 (11.1)	12 (85.7)/2 (14.3)	0.564 <sup>b</sup>
Smokers, n (%)	1 (3.7)	3 (21.4)	0.107 <sup>b</sup>
Coronary artery disease, n (%)	3 (11.1)	2 (14.3)	0.564 <sup>b</sup>
Hypertension, n (%)	13 (48.1)	7 (50)	0.585 <sup>b</sup>
Diabetes mellitus, n (%)	10 (37)	6 (42.8)	0.487 <sup>b</sup>
ACEi or ARB users, n (%)	9 (33.3)	7 (50.0)	0.241 <sup>b</sup>
β-Blocker users, n (%)	6 (22.2)	5 (35.7)	0.286 <sup>b</sup>
CCB (dihydropyridin) users, n (%)	11 (40.7)	4 (28.6)	0.339 <sup>b</sup>
Phosphorus binder users, n (%)	25 (92.6)	10 (71.4)	0.091 <sup>b</sup>
Vitamin D users, n (%)	8 (29.6)	5 (35.7)	0.477 <sup>b</sup>
Erythropoietin users, n (%)	13 (48.1)	3 (21.4)	0.091 <sup>b</sup>
Statin users, n (%)	4 (14.8)	3 (21.4)	0.449 <sup>b</sup>
Kt/V	1.5±0.4	1.5±0.3	0.794 <sup>a</sup>
Albumin, g/dl	3.1±0.5	3±0.6	0.674 <sup>a</sup>
C-reactive protein, mg/l	9.6±12.8	14.5±22.6	0.559 <sup>a</sup>
Parathormone, pg/dl	244.1±183.3	212.4±112.8	0.924 <sup>a</sup>
Hemoglobin, g/dl	11±1.2	11.6±1.1	0.086 <sup>a</sup>
Triglyceride, mg/dl	201±161	147±76	0.674 <sup>a</sup>
Cholesterol, mg/dl	182±66	156±56	0.159 <sup>a</sup>
HDL cholesterol, mg/dl	35±18	28±6	0.422 <sup>a</sup>
LDL cholesterol, mg/dl	96±38	90±48	0.559 <sup>a</sup>

Data are expressed as means ± standard deviation and numbers with percentages in parentheses. ACEi = Angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; AVF = arteriovenous fistula; CCB = calcium channel blockers; HDL = high-density lipoprotein; LDL = low-density lipoprotein; group 1 = patients without increased myocardial injury enzymes during HD; group 2 = patients with increased myocardial injury enzymes during HD. <sup>a</sup> Mann-Whitney U test. <sup>b</sup>  $\chi^2$  test.

### Biochemical Parameters

When biochemical parameters of the patients before and after HD were compared, a statistically significant decrease was found in the levels of BUN, creatinine, potassium, phosphate and blood glucose after HD ( $p < 0.001$ ,  $p < 0.001$ ,  $p < 0.001$ ,  $p < 0.001$  and  $p = 0.027$ , respectively). Statistically significant increases were defined in the levels of calcium, magnesium and bicarbonate ( $p < 0.001$ ,  $p < 0.001$  and  $p < 0.001$ , respectively). No significant difference was found in the levels of sodium between the values before and after HD (table 2). When the markers of myocardial injury were compared, there was a statistically significant increase in the levels of troponin I, myoglobin and CK MB after HD ( $p = 0.019$ ,  $p < 0.001$  and  $p = 0.018$ , respectively). No significant difference was observed in the levels of NT-proBNP between both periods (table 2).

**Table 4.** Change rates of both groups in hemodynamic conventional Doppler and tissue Doppler echocardiographic and biochemical parameters

Variable	Group 1 (n = 27)	Group 2 (n = 14)	p*
Hemodynamic parameters, %			
Systolic blood pressure change	-3.6±15.7	-4.4±23.5	0.924
Diastolic blood pressure change	-0.6±13.7	-5±15.8	0.860
Mean arterial pressure change	-2±14.1	-4.7±18	0.674
Pulse pressure change	-2±14.1	-4.9±18	0.674
Heart rate change	7.7±16.7	14.7±18.1	0.204
PCWP change	-13±23	-7.7±16.3	0.391
Conventional echocardiographic parameters, %			
Stroke volume change	4.4±21.9	1.2±19.1	0.714
EF change	6.9±3.7	9.8±7.8	0.246
Cardiac output change	12.3±28.2	14.8±21.5	0.557
LAV change	-3.2±21.2	-9.9±10.4	0.347
LAD change	-12.7±16.7	-11.8±6.6	0.596
LVEDD change	-6.9±4.7	-7.9±5.7	0.714
LVESD change	-9.4±3.6	-11.8±7.1	0.204
MAPSE change	9±12.7	5.1±23.2	0.185
TAPSE change	-0.3±18	0.3±19.8	0.860
Pulsed-wave Doppler echocardiographic parameters, %			
A change	-2.7±31.2	-6.3±17.7	0.089
E change	-17.8±21.1	-26.2±17.4	0.176
E/A change	-11.1±27.7	-28.7±22.6	<b>0.049</b>
Vp change	13.1±34.3	6.9±27.2	0.615
E/Vp change	-20.7±32.2	-25.7±32.6	0.541
DT change	12.2±37.9	30.6±47.3	0.257
IVRT change	18.8±33.6	11.7±40.2	0.776
Tissue Doppler echocardiographic parameters, %			
Lateral á change	0.02±0.4	0.2±0.3	0.060
Lateral é change	0.05±0.4	-0.15±0.3	0.067
Septal á change	0.04±0.3	0.09±0.2	0.530
Septal é change	-0.01±0.3	-0.13±0.3	0.454
E/é change	-13±26.2	-11.5±16	0.541
LV S' velocity change	12±24.7	-3.6±11.1	<b>0.011</b>
RV S' velocity change	4.1±22.6	6.7±22.3	0.860

Data are expressed as means ± standard deviation of percentages. Bold values indicate statistical significance. Group 1 = Patients without increased myocardial injury enzymes during HD; group 2 = patients with increased myocardial injury enzymes during HD. \* Mann-Whitney U test.

In order to evaluate the statistically significant increases in the levels of troponin I, CK MB and myoglobin, the patients were divided into two groups according to the baseline values before HD, namely patients without an increase in cardiac enzymes compared to the baseline values (group 1) and patients with an increase in cardiac enzymes ( $\geq 50\%$  increase in CK MB, troponin  $>0.04$  ng/ml with an increase in myoglobin; group 2). There was no difference between the groups in terms of age, gender, weight, body mass index, body surface area, the amount of residual urine, excess fluid, HD duration, the amount of ultrafiltrate, vascular access, smoking, presence of coronary artery disease, hypertension or diabetes mellitus, medication, Kt/V, C-reactive protein, albumin, parathormone (PTH), hemoglobin level and lipid profile (table 3).

**Table 5.** Change rates in biochemical parameters of both groups

Variable	Group 1 (n = 27)	Group 2 (n = 14)	p*
Blood urine nitrogen change, %	−66.9±9	−66.9±8.3	0.776
Creatinine change, %	−58.3±12.7	−53.2±12	0.091
Sodium change, %	−0.6±2	0.8±1.7	<b>0.022</b>
Potassium change, %	−30.8±11.5	−25.1±9.4	<b>0.045</b>
Phosphorus change, %	−42.3±19.5	−34.4±23.6	0.347
Calcium change, %	14±8.7	19.8±12.2	0.151
Magnesium change, %	9.5±13.6	16.9±10.8	<b>0.042</b>
Bicarbonate change, %	39.6±24.6	36.6±34.8	0.391
Blood glucose change, %	−3.2±37.7	−14±30	0.307
NT-ProBNP change, %	7.2±29.4	−4.4±15.3	0.235

Data are expressed as means ± standard deviation of percentages. Bold values indicate statistical significance. Group 1 = Patients without increased myocardial injury enzymes during HD; Group 2 = patients with increased myocardial injury enzymes during HD. \* Mann-Whitney U test.

**Table 6.** Multivariate logistic regression analysis of the parameters showed a significant difference in univariate analyses

Variable	B	SE	p	Exp(B)	95% CI for Exp(B)	
					lower	upper
LV S' velocity change, %	−0.094	0.046	<b>0.039*</b>	<b>1.099</b>	1.005	1.202
E/A change, %	−0.025	0.022	0.240	0.975	0.934	1.017
Potassium change, %	0.052	0.057	0.365	1.053	0.941	1.178
Sodium change, %	0.289	0.239	0.227	1.336	0.835	2.136
Magnesium change, %	0.071	0.046	0.116	1.074	0.982	1.174

Bold values indicate 1.099 odds ratio. \* p < 0.05.

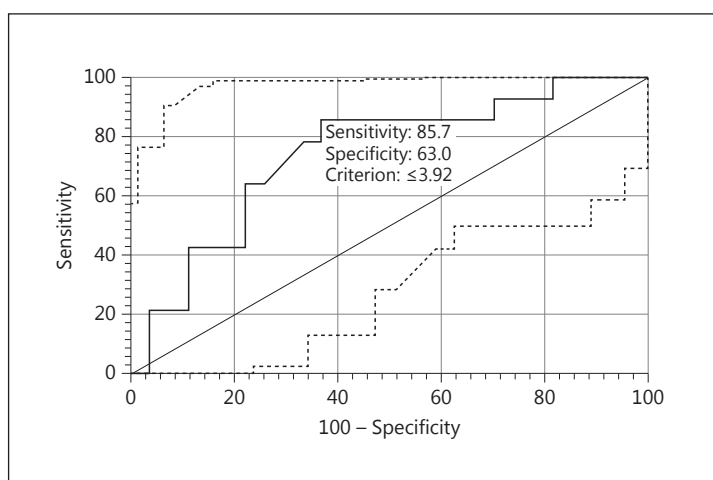
When the change rates in diastolic and systolic parameters defined with hemodynamic examinations, conventional, pulsed-wave Doppler and TDI were compared (table 4), there was a greater difference in E/A in a negative direction with HD in group 2 compared to group 1 (p = 0.049), while LV S' velocity was found to be decreased in group 2 and increased in group 1 (p = 0.011).

When the change rates in electrolyte, blood glucose, bicarbonate and NT-proBNP occurring with HD were compared, a positive increase was found in the change rates of sodium and magnesium levels in group 2, and a less negative change rate in the potassium levels compared to group 1 (p = 0.022, p = 0.042 and p = 0.045, respectively; table 5).

Logistic regression analysis was performed for the LV S' parameter, which is a TDI systolic function parameter, and for E/A change rate, which is a diastolic function parameter, as well as for the change rate in the levels of sodium, potassium and magnesium, in order to explain cause-and-effect relationships. A statistically significant difference was found between the groups (table 6).

As a result of the multivariate logistic regression analysis, change of LV S' velocity in a negative direction was found to be an independent predictor of the increase in the markers of cardiac damage in HD [odds ratio Exp(B) = 1.099; p = 0.039].

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**Fig. 4.** LV S' velocity change rate ROC curve of HD patients with increased myocardial injury enzymes.

On the ROC curve, the cutoff value of the change rate in LV S' velocity which predicted an increase of cardiac enzyme was observed as  $\leq 3.92\%$ , sensitivity as 85.7% and specificity as 63% (area under the curve 0.743; 95% CI 0.583–0.867;  $p = 0.0033$ ; fig. 4).

## Discussion

Cardiovascular events in cases with CKD mostly begin in the predialysis period and increasingly continue during dialysis. This causes a dramatic decrease in the likelihood of survival. There is instability in ESRD patients because of CKD-specific factors such as hypervolemia, activation of the renin-angiotensin-aldosterone system, catecholamines due to sympathetic activation, increase in vasopressin and endothelin, decrease in the activity of nitric oxide, cardiac systolic and diastolic dysfunction, hyperdynamic circulation due to arteriovenous fistula, persistence of diabetes mellitus, CVD, IDH related to the HD procedure and changes in electrolyte levels. Recent studies with ESRD patients have focused on the clinical and epidemiological issues such as diagnosis, context, prognosis and treatment of CVD because of the high cardiovascular mortality.

TDI enables evaluation of cardiac functions by analyzing the myocardial velocities and allows assessment of global, segmental, systolic and diastolic functions of the ventricles in clinical practice. In this respect, it can provide more and crucial additional data about global and segmental myocardial changes than conventional echocardiography in HD patients. It has been suggested that acute major volume changes in HD patients are associated with  $\dot{e}$  velocity, that the  $E/\dot{e}$  ratio is a parameter independent of the volume load in the evaluation of left ventricular functions and that only conventional evaluation of left ventricular systolic and diastolic functions is not sufficient; therefore, left ventricular functions should be further evaluated with the TDI method as this technique is more sensitive than conventional echocardiography for the evaluation of left ventricular functions [32, 33].

It has been demonstrated in tissue Doppler echocardiographic examination that  $\dot{e}$ ,  $\dot{a}$  and LV S' velocity, which are the parameters of diastolic and systolic functions, significantly decrease compared to before HD, that  $\dot{e}$  velocity is a marker of left ventricular diastolic dysfunction independent of the preload and that an acute impairment occurs in myocardial diastolic and systolic function parameters even in a single HD session. These changes were reported to be a reversible cardiac stunning [34, 35]. Drighil et al. [36] reported a decrease in

left ventricular septal  $\epsilon$  and RV S' velocity following HD. E/Vp and E/ $\epsilon$  rates are associated with left ventricular filling pressure [37]. In their study, including 220 HD patients, Wang et al. [38] reported that E/ $\epsilon$  rates were increased in 62% of the cases and demonstrated that this increase was an independent predictor of cardiovascular and all-cause mortality. Li et al. [39] reported that parameters such as E/ $\epsilon$  and LAV, which are indicators of diastolic functions, were significantly high in HD patients and diastolic dysfunction developed in 85% of the cases, while LV S' velocity, which is one of the systolic function parameters, was significantly low. In patients on HD therapy with preserved systolic function, decreased LV S' velocity has been found to be an independent predictor of left ventricular filling pressure. Therefore, it has been proposed to better monitor LV S' velocity and to use it in the planning of the treatment for these patients in the daily practice [40].

In this study, we observed a decrease in diastolic parameters such as E, E/A and E/Vp, and an increase in systolic parameters such as MAPSE, LVEDD, LVESD, LAV, EF and cardiac output following HD. We found a decrease in septal  $\epsilon$  and E/ $\epsilon$  parameters. There was a decrease also in PCWP. No significant difference was found in LV S' and RV S' velocities. These data can be interpreted as follows: HD led to an improvement in systolic functions and to an impairment in diastolic functions.

Troponins are accepted as the 'gold standard' indicators in the diagnosis of ischemic myocardial damage [41]. Troponins often increase in cardiac-asymptomatic patients. These high levels of troponin have been defined to be associated with an increased mortality [18, 19]. The key question to be answered on this subject is whether this increase results from myocardial damage or from the metabolism or whether clearance has changed due to renal failure. In a study including marathon runners, chronic HD patients and patients with acute and chronic skeletal muscle damage it was reported that, independent of acute and chronic skeletal muscle damage, the levels of CK MB increased, while troponin levels did not increase unless there was cardiac damage [42]. In many studies, troponin increase in CKD has been reported to be of cardiac origin [43, 44]. In 244 patients without acute coronary syndrome who regularly received HD, a correlation was shown between high values of troponin and all-cause mortality [45]. In a study investigating the incidence of repeated subclinical myocardial damage due to HD and the effects of HD on long-term left ventricular functions in a period of 12 months, significant myocardial stunning was found in 64% of the patients during HD, and age, ultrafiltration volumes, IDH and increased levels of troponin T were reported as independent predictors of myocardial stunning. In the same study, increased mortality was found to be associated with myocardial stunning [46].

At the end of a 1-year follow-up period, Burton et al. [47] found in many HD patients myocardial segments in which systolic function was decreased. There were significant decreases in left ventricular EF during the resting period in this group of patients. In the conclusion of the study, myocardial segments with systolic dysfunction were suggested to result from myocardial stunning caused by HD at the end of a 12-month period and it was suggested that this condition was associated with underlying myocardial fibrosis and hibernation. It was stated that this might be a potentially changeable important process in the development of cardiac failure in HD patients [47]. In a study by McIntyre et al. [48] using positron emission tomography, myocardial blood flow that was normal before HD was found to be globally acutely decreased during HD resulting in regional wall motion abnormalities. The study demonstrated that wall motion abnormality occurred in the segments with >30% decrease in myocardial blood flow compared to the baseline. In the conclusion of the study, the authors reported that HD was associated with repeated myocardial ischemia in the absence of coronary artery disease, and this might be caused by coronary microvascular dysfunction [48, 49].



In the present study, a significant increase was found in CK MB, myoglobin and troponin I level following HD. NT-proBNP levels decreased because of a reduction in preload due to ultrafiltration. However, no difference was found in NT-proBNP levels between both groups compared to baseline values before HD. Furthermore, no IDH was found in either group. According to our data, the increase in CK MB, myoglobin and troponin I did not develop secondary to the sharp loss of volume and blood pressure changes.

In addition, a decrease in the E/A ratio was defined in both groups, which was greater in those with an increase of cardiac enzyme after HD. There was a decrease in LV S' velocity in group 2 and an increase in group 1. These data indicate that the increase of cardiac enzyme was correlated with tissue Doppler echocardiography parameters and associated with diastolic and systolic dysfunction.

Increased levels of troponin in cardiac-asymptomatic HD patients were reported to be caused by continuously repeated and silently developed small infarcts due to underlying CVD [50]. Persistence of myocardial small infarct areas was shown in patients with high levels of troponin [51]. Considering the high incidence of CVD in HD patients, persistent and/or repeated microepisodes of silent infarction are likely to occur [50]. Although different results have been reported in various studies evaluating CK MB, myoglobin and troponin levels in asymptomatic CKD patients on HD, it is noteworthy that there is a consensus in these studies that the troponin increase compared to the baseline value should be used for the diagnosis of myocardial damage and that increased levels of troponin predict mortality, thus having a prognostic value [52–54].

In 1,549 oligoanuric HD patients in the randomized HEMO study, the risk ratio for all-cause mortality was found to be 0.84 for each 4 mEq/l increase of basal predialysis serum sodium concentration. In that study, demographic, clinic and other laboratory values and dialysis-specific common variables, including the amount of ultrafiltration, did not show a difference [55]. In a study investigating long-term variability in serum sodium of HD patients, no significant change was observed in serum sodium of 100 HD patients in the 12-month follow-up period [56]. Both hypopotassemia and hyperpotassemia were found to be associated with cardiovascular and all-cause mortality [57, 58]. It was reported that the survival was highest in patients with a serum level of potassium between 4.6 and 5.3 mM before HD, while a serum level of potassium <4.0 or >5.6 mM was associated with increased mortality, and a high dialysate potassium concentration was associated with increased mortality in the patients with a serum level of potassium >5.0 mM. It is yet to be determined whether the high mortality rate that was found to be associated with a high serum level of potassium before HD was due to a predialysis abnormality itself or whether the potassium fluctuations developed during HD [59, 60]. Changes in potassium levels depend on the distribution between two compartments and are in contrast to urea; potassium makes a marked rebound after HD. In this respect, we cannot estimate the postdialysis potassium level based on cleaning of a solute from a single pool. The decrease rate of the potassium level during HD is associated with the predialysis potassium level. This depends not only on the reduction of increased potassium, but also on the potassium distribution volume. Therefore, we cannot assume a fixed distribution volume for a single pool or for this ion when estimating the effect of HD on the plasma concentration of potassium [61].

Magnesium plays an important role in the transport of  $\text{Na}^+/\text{K}^+$  by activation of the  $\text{Na}^+/\text{K}^+$ -ATPase pump. Thus, a decrease of the cellular magnesium was found to lead to a reduction of potassium in many cells, including cardiac and vascular muscle cells [62]. It has been argued in numerous experimental and clinical trials that magnesium deficiency may cause an increase in the intracellular calcium concentration of cardiac myocytes, occurrence of reactive oxygen species, release of proinflammatory cytokines and growth factors, and resultant changes in membrane permeability in cardiac cells and may lead to changes in transport

processes causing atherosclerosis, arrhythmias, ischemic heart disease, congestive heart disease and sudden cardiac death [63, 64].

In our study, a correlation was observed between the increase in cardiac enzyme after HD and the increase in the serum levels of sodium and magnesium. However, the increase of cardiac enzyme after HD was associated with a lower rate of decrease in the serum level of potassium. The lower rate of decrease in group 2 may have been caused by decreased levels of potassium and increased levels of magnesium before HD.

The change that occurred in the levels of sodium, potassium and magnesium during HD was associated with an increase in cardiac enzymes. This form of change in the levels of sodium, potassium and magnesium may result in diastolic and systolic dysfunction, contributing to myocardial damage with negative effects on hemodynamic instability and myocardial contractility. However, in a multivariate analysis of the changes in the levels of sodium, potassium and magnesium, and changes in the E/A ratio and LV S' velocity, only change in LV S' velocity, which is a TDI left ventricular systolic function parameter, was found to be an independent predictor of increased myocardial injury enzymes. This suggests that HD may impair systolic function, leading to myocardial damage.

High levels of troponins in CKD are cardiac induced and, whether or not symptomatic, they are associated with an increased mortality rate. Regardless of the origin and cause, explaining the high levels of troponin only with a decrease in kidney clearance does not seem very likely because, since both free and bound troponin have a large molecular structure (like albumin), it is thought that the clearance cannot be largely due to the kidneys. Furthermore, half-life of troponin I following AMI is not different in persons with normal renal function and ESRD patients, supporting this prediction [65].

## Conclusion

The data from this study support the occurrence of myocardial damage in HD. Although similar data were obtained in numerous studies, so far the pathophysiology has not been fully explained. This may be related to myocardial ischemia and myocardial microinfarcts resulting from an impairment in myocardium physiology and myocardial blood flow caused by hemodynamic and electrolyte changes occurring during HD. We believe that systolic dysfunction identified with TDI during HD leads to myocardial damage. In this respect, cardiac functions of HD patients should also be evaluated with TDI. It should be considered that HD may lead to stress; adverse cardiac effects of HD should be taken into account, especially when acute HD is chosen in cardiac and hemodynamically unstable patients; the cardiovascular risk profile of CKD patients should be determined and the treatment plans of the patients with a high cardiovascular risk profile and systolic and/or diastolic dysfunction should be individualized.

Given the high cardiovascular mortality in ESRD, we believe that further detailed multicenter studies with a greater number of patients should be conducted in order to prevent or minimize the adverse cardiovascular effects of HD, to clarify the pathophysiology, to develop new HD methods and treatment plans and to generate new ideas about cardioprotection in HD patients.

## Disclosure Statement

There are no conflicts of interest.



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