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THE CORRELATION OF LEFT VENTRICULAR MECHANICAL DISPERSION AND LEFT VENTRICULAR EJECTION FRACTION WITH QT DISPERSION IN END-STAGE RENAL DISEASE PATIENTS ON HEMODIALYSIS BEFORE AND AFTER DIALYSIS

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ABSTRACT

***Background**: Ventricular arrhythmias (VA) is common in dialytic patients. Left Ventricular Mechanical Dispersion (LVMD) could provide an inhomogeneous left ventricular myocardium contraction leading to VA. Reduced Left Ventricular Ejection Fraction (LVEF) and QT Dispersion (QTd) are well-known VA predictors in dialytic patients. This study aimed to determine the relationship between LVMD and LVEF on QT dispersion in ESRD patients before and after dialysis.*

***Methods**: This cross-sectional study was conducted from November 2021 - February 2022. All study subjects who met the inclusion criteria underwent history taking and physical examination including age, sex, body weight, body height, electrocardiography, echocardiography, and routine laboratory studies.*

***Results**: Among 43 subjects, 24 (55.8%) were male, with a mean age of 51,14±11,6 was conducted in this study. The most common comorbidities were hypertension (79%) and diabetes mellitus (44.19%). Pre-dialysis LVMD mean was 28.99±15.98 ms and significantly decreased to 24.16±15.77 ms after dialysis ($p<0.05$). There was an insignificant decrease in the QTd value before dialysis with a mean of 61.72±25.93 ms to 54.60±21.26 ms. There was no difference between the mean LVEF before and after dialysis (57.19±5.17%) and after dialysis (57.54±5.04%). There is no correlation between LVEF, LVMD and QTd variables before and after dialysis.*

***Conclusion**: There was a significant decrease in LVMD after the dialysis period, but there was no significant difference in the LVEF and QTd parameters. No correlation was found between QTd parameters, LVMD, or LVEF in ESRD patients on HD both before and after dialysis.*

***Keywords:** Sudden cardiac death, end-stage renal disease, hemodialysis, left ventricular mechanical dispersion, left ventricular ejection fraction, QT dispersion.*

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ABSTRAK

Latar Belakang: Kejadian aritmia ventrikular cukup sering pada pasien yang menjalani dialisis. *Left Ventricular Mechanical Dispersion* (LVMD) menggambarkan kontraksi miokardium ventrikel kiri yang tidak homogen dan berisiko menyebabkan aritmia ventrikular. Penurunan fraksi ejeksi ventrikel kiri dan *QT Dispersion* (QTd) adalah prediktor aritmia ventrikel yang telah banyak dikenal pada populasi pasien dialisis. Penelitian ini bertujuan untuk mengetahui hubungan antara LVMD dan fraksi ejeksi ventrikel kiri terhadap dispersi QT pada pasien gagal ginjal stadium lanjut sebelum dan sesudah dialisis.

Metode: Studi ini memiliki desain potong lintang dan dilakukan pada November 2021 - Februari 2022. Semua subjek studi yang memenuhi kriteria inklusi menjalani pengambilan riwayat dan pemeriksaan fisik termasuk usia, jenis kelamin, berat badan, tinggi badan, elektrokardiografi, ekokardiografi, dan studi laboratorium rutin.

Hasil: Di antara 43 subjek, 24 (55,8%) adalah laki-laki, dengan usia rata-rata 51±11,6 tahun. Komorbiditas yang paling banyak antara lain hipertensi (79%) dan diabetes melitus (44,19%). Rerata LVMD pra-dialisis adalah 28,99±15,98 ms dan menurun secara signifikan menjadi 24,16±15,77 ms setelah dialisis ($p<0,05$). Terjadi penurunan nilai QTd yang tidak signifikan sebelum dialisis dengan rata-rata 61,72±25,93 ms menjadi 54,60±21,26 ms. Tidak ada perbedaan dalam rerata fraksi ejeksi ventrikel kiri sebelum (57,19±5,17%) dan setelah dialisis (57,54±5,04%). Tidak ada korelasi antara variabel fraksi ejeksi ventrikel kiri, LVMD dan QTd sebelum dan sesudah dialisis.

Kesimpulan: Terdapat penurunan LVMD yang signifikan setelah periode dialisis, tetapi tidak ditemukan perbedaan yang signifikan pada parameter fraksi ejeksi ventrikel kiri dan QTd. Tidak ada korelasi yang ditemukan antara parameter QTd, LVMD, atau fraksi ejeksi ventrikel kiri pada pasien gagal ginjal stadium lanjut baik sebelum maupun sesudah dialisis.

Kata kunci: Kematian jantung mendadak, penyakit ginjal stadium akhir, hemodialisis, dispersi mekanik ventrikel kiri, fraksi ejeksi ventrikel kiri, dispersi QT.

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INTRODUCTION

End-stage renal disease (ESRD) is advanced-stage renal failure with glomerular filtration rate (GFR) below 15 ml/min/1.73 m^2. The prevalence of ESRD patients is increasing after the discovery of

hemodialysis methods that increase life expectancy but the cardiovascular mortality rate in these patients remains high. Data shows that hemodialysis patients in Indonesia have increased by three times from 2007 to 2011.[1] Basic Health Research Data 2018 (Riskesdas) shows an increase in the prevalence rate to 3.8‰ (per mile) which is 713,783 people when compared to 2013 which was only 2‰ or 499,800 people. North Sulawesi accounts for 6,827 patients from the total population of kidney failure patients in Indonesia and its prevalence is 5.3‰, higher than the national prevalence.[2]

Heart rhythm disturbances in the form of ventricular arrhythmias in ESRD patients undergoing hemodialysis (HD) can cause sudden death up to 30% of all causes.[3] In several previous studies, ventricular arrhythmias are associated with acetate buffered fluids and low potassium dialysate fluids (< 2.0 mmol/L) which have proarrhythmic properties.[4] However, after changing the composition of the dialysate and buffer, the sudden death rate in ESRD patients is still high. Arrhythmia in the form of non-sustained ventricular tachycardia (NSVT) detected by examination of implantable loop recorders for three months was experienced by 14%-57% of ESRD patients who routinely underwent HD. Patients with ESRD will experience structural changes in the myocardium that act as proarrhythmic substrates that trigger life-threatening arrhythmias.[5]

Left Ventricular Mechanical Dispersion (LVMD) is a new parameter that can be used to describe the inhomogeneity of left ventricular myocardium contractions. This examination is obtained by echocardiography and describes the mechanical dispersion and discoordination that occurs when the heart muscle contracts. The higher the LVMD value, the higher the mechanical dyssynchrony process of the left ventricle which is associated with life-threatening left ventricular arrhythmias. These parameters are relatively affordable, simple and easy to perform by clinicians.[6]

Left ventricular ejection fraction (LVEF) is a predictor of sudden cardiac death with a cut-off of 48% with a specificity of 78.6% (95% CI: 72.2% to 84.1%) and a sensitivity of 57.7% (95% CI: 36.9% to 76.6%) in a previous study involving ESRD patients. QT dispersion (QTd) is a marker of myocardial electrical instability. An increased variation in the QT interval is associated with sudden death from ventricular arrhythmias in patients with heart failure.[7]

In ESRD patients who have experienced structural changes of the myocardium, these two relatively simple examinations using echocardiography and electrocardiogram may be a relatively

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affordable, easy and prognostic test to predict the incidence of sudden cardiac death in ESRD patients on HD.

From those mechanism above, early recognition of proarrhythmogenic substrates that can trigger left ventricular arrhythmias in ESRD patients on HD is important. No studies that have assessed the correlation between LVMD and LVEF in ESRD patients on HD before and after HD. This study found a correlation between LVMD, LVEF, and QT dispersion in ESRD patients on HD before and after HD in Indonesia, especially in North Sulawesi.

METHOD

This research was an observational analytic study with a cross-sectional approach. All patients with chronic kidney failure at the Prof. dr. R. D. Kandou Hospital Manado who underwent hemodialysis from November 2021 to February 2022 and met the inclusion criteria are included in this study using a consecutive sampling method. Information and an examination were conducted to determine the relationship between LVMD and LVEF on QTd in the period before and after HD. The collection of information from the subjects began after the researchers obtained the approval of the Ethics Committee of the RSUP Prof. dr. R. D. Kandou Manado.

Inclusion criteria included the following conditions: Chronic renal failure undergoing hemodialysis < 3 years with age < 70 years with EF ≥ 50%, age over 17 years, having laboratory data before (at long interdialytic interval > 48-72 hours) and after HD (more than 12-24 hours after the HD was performed), did not have severe valvular heart disease, on sinus rhythm, and were willing to undergo echocardiography and electrocardiogram examinations. Exclusion criteria included the following: acute heart failure condition, ventricular or supraventricular arrhythmias or atrial fibrillation on the resting ECG, QRS duration > 120 ms, patients with severe electrolyte disturbances (K < 2 mEq/L or > 6 mEq/L and Magnesium < 1.2 mEq/L or taking drugs that prolong the QT interval (amiodarone, fluoroquinolones, or macrolides), using cardiac pacemaker, or were uncooperative and unwilling to participate in the study.

Electrocardiogram examination used Fukuda Cardimax FCP-8100 and echocardiography examination used Philips Epiq 5.

The differences in LVMD, LVEF, and QT dispersion values before and after dialysis were analyzed using paired t-test or Wilcoxon signed-rank test. Modeling the correlation between LVMD and LVEF variables with the QTd variable as an outcome was planned using the Pearson or

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Spearman correlation test. P value < 0.05 (95% confidence interval) was considered statistically significant.

RESULT

Forty-three ESRD patients on HD were included in the study from November to February 2022, more than half of whom were male (55.8%). The mean age was at 51.14 ± 11.6 years. The basic characteristics of the research subjects are shown in table 1.

Table 1 Characteristics of ESRD patients on HD in the study (N=43)

Characteristics	**Mean ± SD**	**Median**	**IQR**	**n (%)**
Age (years)	51.14 ± 11.63	54 (46-58)	12	
Sex				
Male	-	-		24 (55.8%)
Female	-	-		19 (44.2%)
Height (cm)	159.9 ± 7.1	-		-
Weight (kg)	-	58 (49-65)	16	-
BSA Mosteller (m^2)	-	1.61 (1.47-1.71)	0.24	
Previous comorbidities				
Hypertension	-	-		34 (79%)
Ischemic stroke	-	-		2 (4.65%)
Hemorrhagic stroke	-	-		0 (0%)
Diabetes Melitus	-	-		19 (44.19%)
Coronary artery disease	-	-		4 (9.3%)
Current medications				
Beta-blockers	-	-		13 (30.2%)
Digoxin	-	-		0 (%)
Calcium channel blockers	-	-		35 (81.4%)
ACE inhibitors	-	-		2 (4.6%)
Angiotensin Receptor Blockers	-	-		29 (67.4%)
Diuretics	-	-		15 (34.8%)
Statins	-	-		7 (16.3%)

Note: SD standard deviation, ;BSA *body surface area*; ACE, *angiotensin-converting enzyme; TOR interquartile range*

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Table 2 Characteristics of echocardiographic, laboratory, and electrocardiographic measurement in the study

Parameters	Pre HD (n=43)		Post HD (n=43)		p
	Mean	Median	Mean	Median	
Echocardiographic parameters					
LVEF (%)	-	55.5 (52.6-60.3)	-	56.4 (53.6-61.5)	0.381
GLS (%)	-16.2 ± 2.2	-	-15.6 ± 2.2	-	**0.014**
LVMD (ms)	-	29 (15.3-37)	-	23.1 (9.7-33)	**0.000**
LVMI (g/m2)	-	143 (120-163)	-	137 (107-163)	0.310
PWd (cm)	1.2 ± 0.2	-	1.21 ± 0.25	-	0.631
LVEDD (cm)	5.2 ± 0.6	-	5.12 ± 0.6	-	0.401
IVSd (cm)	-	1.03 (0.8-1.3)	-	1.03 (0.76-1.22)	0.271
RWT	0.46 ± 0.1	-	0.48 ± 0.1	-	0.461
E/E' septal	-	14.2 (11.9-19.2)	-	14.5 (10.8-20.1)	0.648
E/E' lateral	12.5 ± 4.8	-	-	12.7 (8.1-16.8)	0.300
E/A	-	1.1 (0.9-1.3)	-	1.1 (0.8-1.3)	0.535
TAPSE (cm)	2.3 ± 0.4	-	-	2.2 (2.1-2.4)	0.199
Laboratory parameters					
WBC ($x10^3/\mu L$)	6.75 ± 2.3	-	7.03 ± 2.1	-	0.377
Hgb (g/dL)	8.6 ± 1.1	-	-	8.6 (8.1-9.1)	0.727
Na (mEq/L)	-	135 (133-138)	133 ± 5.4	-	0.366
K (mEq/L)	4.9 ± 0.8	-	-	4.6 (4.2-5.1)	**0.000**
Ca (mEq/L)	-	9.1 (8.3-10.1)	9.9 ± 1.3		**0.000**
Mg (mEq/L)	-	2.55 (1.9-3.4)	-	2.74 (1.68-3.4)	0.308
Ureum (mg/dL)	-	125 (108-156)	-	88 (70-122)	**0.000**
Creatinine (mg/dL)	-	10 (8.4-11.7)	-	7.4 (6.5-9.2)	**0.000**
Albumin (g/dL)	4.04 ± 0.4	-	4 ± 0.5		0.199
Electrocardiographic parameters					
QT (msec)	413.3 ± 42.3	-	-	402 (381-431)	0.566
QTcB (msec)	456.9 ± 21.9	-	450.7 ± 22.5	-	**0.030**
QTcF (msec)	-	446 (426-460)	-	431 (420-448)	0.065
QTD (msec)	-	56 (44-74)	54.6 ± 21.3	-	0.109

Note: HD hermodialysis, LVEF *left ventricular ejection fraction*. GLS *global longitudinal strain*. LVMD *left ventricular mechanical dispersion*. LVMI *left ventricular mass index*. PWd *posterior wall diameter*. LVEDD *left ventricular end-diastolic diameter*. IVSd *interventricular septum at and diastole diameter.*. RWT *regional wall thickness*. TAPSE *tricuspid annular plane systolic excursion*. WBC white blood cell Hb hemoglobin. Na sodiumum. K potassium, Ca, calsium. Mg magnesium. QTcB *QT corrected Bazzet*. QTcF *QT corrected* Fridericia. QTD QT dispersion

There was no significant difference between LVEF before and after dialysis (p= 0.381). (table 3)

Table 3 Wilcoxon signed-rank test for the differences in LVEF pre and post HD

	LVEF Post HD - LVEF Pre HD
Z	-.875
p	.381

Note: LVEF, *left ventricular ejection fraction*

In ESRD patients on HD. the LVMD pre-HD value had a median of 29 ms (IQR 21.7 ms) and decreased to a median of 23.1 ms (IQR 23.3 ms) after dialysis (table 1). Nonparametric comparative analysis using the Wilcoxon signed-rank test. showed a significant difference with $p < 0.05$. (table 4)

Table 4 Wilcoxon signed-rank test for the differences in LVMD pre and post HD

	LVMD Post HD - LVMD Pre HD
Z	-3.592
p	.000

QTd measurements before dialysis showed a median value of 56 ms (IQR 30 ms) and decreased to 51 ms (IQR 28 ms) after dialysis (table 4). However. the difference in QTd before and after dialysis was statistically insignificant with p=0.109 (table 5).

Table 5 Wilcoxon signed-rank test for the differences in QTd pre and post HD

	QTd Pre HD - QTd Post HD
Z	-1.601
p	.109

Spearman's correlation analysis for the parameters before dialysis showed that LVEF pre HD and LVMD pre HD did not significantly correlated with p=0.266. Pre HD QTd examination also did not show a significant correlation with LVEF with p=0.928. QTd pre HD with LVMD pre HD also found no significant correlation with p=0.707. (table 6).

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Table 6 Spearman's Correlation Analysis before dialysis for LVEF. LVMD and QTd

		LVEF	LVMD	QTd
LVEF	r		-.173	.014
	p		.266	.928
	N		43	43
LVMD	r	-.173		.059
	p	.266		.707
	N	43		43
QTd	r	.014	.059	
	p	.928	.707	
	N	43	43	

Note: LVEF, left ventricular ejection fraction; LVMD, left ventricular mechanical dispersion; QTd, QT dispersion

Parameters after dialysis showed that post HD LVEF had a median of 56.4% (IQR 7.9%). post HD LVMD with a median of 23.1 ms (IQR 23.3 ms). and post HD QTd with a median of 51 ms (IQR 28 ms). (table 1). After analyzing the correlation for the parameters after dialysis using Spearman's correlation analysis. it was found that post HD LVEF and post HD LVMD did not have a significant correlation with p = 0.738. Post HD QTd examination also did not show a significant correlation with post HD LVEF with p = 0.528. QTd post HD with LVMD post HD also did not show a significant correlation with p = 0.261. (table 7).

Table 7 Spearman's Correlation Analysis after dialysis for LVEF. LVMD and QTd

		LVEF	LVMD	QTD
LVEF	r		-0.053	0.099
	p		0.738	0.528
	N		43	43
LVMD	r	-0.053		-0.175
	p	0.738		0.261
	N	43		43
QTD	r	0.099	-0.175	
	p	0.528	0.261	
	N	43	43	

Note: LVEF, left ventricular ejection fraction; LVMD, left ventricular mechanical dispersion; QTd, QT dispersion

DISCUSSION

Forty-three ESRD patients on HD are included in this study subjects with a mean age of 51.14 ± 11.63 years. Most patients are in the 4th and 5th decade range, similar to the prevalence of ESRD in Indonesia based on the 2018 Indonesian Renal Registry data. The distribution of sex with male dominance at 55.8% shows that the prevalence of men and women for ESRD patients is fairly distributed. Research subjects have hypertension (79%), and diabetes mellitus (44.19 %) this is also in accordance with prevalence data in Indonesia, where hypertension and diabetes mellitus are the most common causes of end-stage renal failure.[8]

There had been a change in cardiac geometry towards concentric LVH with a mean RWT of 0.46 cm and a median LVMI of 143 grams/m2 (IQR 43 grams/m2). The course of ESRD will cause volume and pressure overload. Compensation in the form of concentric LVH with good left ventricular systolic function was obtained in this study subject with an average LVEF of 57.19% ± 5.17% in this study subjects who did dialysis in the first three years.

The mean of the study subjects had shown an increase in the median E/E' septal at 14.2 (IQR 7.33) and the median E/E' lateral at 12.5 ± 4.8, which is one of the signs of diastolic dysfunction that have occurred in most of ESRD patients on HD.[9] Although the LVEF in the study subjects still showed preserved EF, the GLS obtained drecreased with a mean of -16.22% ± 2.19%. This shows that the strain analysis echocardiographic parameter technique can detect abnormalities earlier in LV systolic function. The form derivative analysis of the strain in the form of LVMD in the study subjects showed the mean at 28.9 ± 15.9 ms. Based on the normal range value per LVMD age by Rodriguez et al., at the age of 40-50 years, the normal value is 34 ± 10 ms.[10]

QT prolongation almost always occurs in ESRD patients on HD and is strongly affected by the electrolyte variability that influences the phases of ventricular depolarization and repolarization. The subjects in this study obtained a mean QTc Bazzet at 456 ms ± 21 ms before HD was performed. Nie et al., stated that the prolongation of the Bazzet QTc and QTd value in ESRD patients on HD is also associated with LVH, a left atrial diameter, and associated with an increase in left ventricular end-diastolic pressure. After calculating the QT dispersion, the mean was 61.72 ± 25.93 ms before dialysis. In Tong et al.'s study, the normal OTd threshold was proposed was proposed at 40-50 ms with approximately the same subjects as this study.[11] Before dialysis was performed, there was an increase in QTc Bazzet and QTd in the subjects of this

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study. The mechanism thought to play a role is an increase in ventricular wall stress resulting in ventricular dilatation and fibrosis.

ESRD patients on HD have myocyte hypertrophy, myocardial fibrosis, and myocardial, increasing ventricular repolarization heterogeneity.[12] Patients with ESRD on HD who still have normal left ventricular ejection function already have subtle myocardial dysfunction. This subtle myocardial dysfunction theoretically will result in a change in the strain analysis that should show an abnormality before a decrease in LVEF occurs.

In this study, there was a significant decrease in LVMD values in the period after dialysis compared to before dialysis. ESRD patients on HD in the period before dialysis usually experience fluid retention, salt, high sympathetic nerve activation, and milieu uremicum conditions. Myocardial strain analysis is more sensitive to changes in volumetric conditions. Another thing that considered to have contributed is hypertension and myocardial hypertrophy, which will increase the instability of the action potential and dysregulation of the excitation-contraction coupling.[13] This is consistent with the significant decrease in the LVMD value after dialysis, which indicates an improvement in the volumetric condition, although there is no change in the LVEF value before and after dialysis. This study is also consistent with Rahman et al., who stated that LVMD as a derivative of strain analysis could detect myocardial function earlier than LVEF.[14]

Several studies with ESRD on HD study subjects performed QTd and QTc Bazzet examinations right after dialysis and found significant QTd and QTc Bazzet prolongation correlated with an increased risk of sudden cardiac death. Bazzet's QTc prolongation is correlated with myocardial structural changes, whereas QTd is more associated with acute changes in electrolytes, hemodynamics, and milieu uremicum during dialysis.[12]

This study differs from other studies that carried out OTd examination in the place right after dialysis and used 12-24 hours after dialysis was performed. The absence of significant QTd changes confirms that the 12-hour period after HD is no longer a vital period for sudden cardiac death due to electrolyte disturbances that act as a trigger for life-threatening arrhythmias.[15]

CONCLUSION

There was a decrease in LVMD values in the post-dialysis period compared to the pre-dialysis period in ESRD patients on HD. In contrast, there was no difference between before and after dialysis in LVEF and QTd values. There is no correlation between LVMD and LVEF parameters with QTd of ESRD patients on HD both before and after dialysis.

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