Turkish Journal of Thoracic and Cardiovascular Surgery 2019;27(3):320-328
http://dx.doi.org/doi: 10.5606/tgkdc.dergisi.2019.17568

Original Article / Özgün Makale

The mid-term effect of left ventricular assist devices on renal functions

Sol ventrikül destek cihazlarının orta dönem böbrek fonksiyonları üzerine etkisi

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ABSTRACT

Background: In this study, we aimed to investigate the mid-term effects of left ventricular assist devices on kidney functions.

Methods: Between January 2015 and December 2017, a total of 61 patients (53 males, 8 females; mean age 46.4±11.2 years; range, 20 to 67 years) who underwent left ventricular assist device implantation were retrospectively analyzed. Glomerular filtration rate was evaluated preoperatively and at 24 and 48 h, at one week, and at one, three, and six months postoperatively. According to the preoperative glomerular filtration rates, the patients were divided into three groups: glomerular filtration rates ≤60 mL/min/1.73 m^2 (Group 1), glomerular filtration rates 61-90 mL/min/1.73 m^2 (Group 2), and glomerular filtration rates >90 mL/min/1.73 m^2 (Group 3).

Results: In all groups, the glomerular filtration rate significantly increased at one week and one month postoperatively, compared to preoperative values ($p<0.001$ and $p<0.01$, respectively). However, the glomerular filtration values at six months significantly decreased, compared to the values at one week and one month postoperatively ($p<0.001$ and $p<0.001$, respectively). The most significant drop to preoperative values was observed in Group 3 ($p=0.02$) at three months and it dropped below the preoperative level at six months ($p<0.001$).

Conclusion: Our study results suggest that left ventricular assist devices can significantly increase the glomerular filtration rate in short-term, irrespective of baseline values. However, this improvement may recede later, particularly in patients with normal renal functions, and it may even disappear following the third postoperative month.

Keywords: End-stage heart failure, glomerular filtration rate, mechanical assist device, renal failure.

ÖZ

Amaç: Bu çalışmada, sol ventrikül destek cihazlarının böbrek fonksiyonları üzerindeki orta dönem etkileri araştırıldı.

Çalışma planı: Ocak 2015 - Aralık 2017 tarihleri arasında sol ventrikül destek cihazı implantasyonu yapılan toplam 61 hasta (53 erkek, 8 kadın; ort. yaş: 46.4±11.2 yıl; dağılım, 20-67 yıl) retrospektif olarak incelendi. Glomerüler filtrasyon hızı ameliyat öncesinde ve ameliyat sonrası 24. ve 48. saatlerde, birinci haftada ve birinci, üçüncü ve altıncı ayda değerlendirildi. Ameliyat öncesi glomerüler filtrasyon hızlarına göre, hastalar üç gruba ayrıldı: Glomerüler filtrasyon hızı ≤60 mL/dk/1.73 m^2 (Grup 1), glomerüler filtrasyon hızı 61-90 mL/dk/1.73 m^2 (Grup 2) ve glomerüler filtrasyon hızı >90 mL/dk/1.73 m^2 (Grup 3).

Bulgular: Grupların tümünde glomerüler filtrasyon hızı, ameliyat öncesi değerlere kıyasla, ameliyat sonrasında birinci hafta ve birinci ayda anlamlı düzeyde arttı (sırasıyla $p<0.001$ ve $p<0.01$). Ancak, ameliyat sonrası birinci hafta ve birinci aya kıyasla, altıncı ayda glomerüler filtrasyon değerleri anlamlı düzeyde azaldı (sırasıyla $p<0.001$ ve $p<0.001$). Ameliyat öncesi değerlere göre en anlamlı düşüş, üçüncü ayda Grup 3'te gözlendi ($p=0.02$) ve ameliyat sonrası altıncı ayda ameliyat öncesi düzeyin altına indi ($p<0.001$).

Sonuç: Çalışma sonuçlarımız, başlangıç değerlerinden bağımsız olarak, sol ventrikül destek cihazlarının kısa dönemde glomerüler filtrasyon hızını anlamlı düzeyde artırabildiğini göstermektedir. Bununla birlikte, bu iyileşme, özellikle böbrek fonksiyonları normal olan hastalarda daha sonra geri dönebilmekte ve hatta ameliyat sonrası üçüncü aydan itibaren gerileyebilmektedir.

Anahtar sözcükler: Son dönem kalp yetmezliği, glomerüler filtrasyon hızı, mekanik destek cihazı, renal yetmezlik.

Received: November 19, 2018 *Accepted:* March 31, 2019 *Published online:* June 14, 2019

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Cite this article as:
Gürcü ME, Altaş Yerlikhan Ö, Özer T, Erkılınç A, Altınay E, Erdem E, et al. The mid-term effect of left ventricular assist devices on renal functions. Turk Gogus Kalp Dama 2019;27(3):320-328

The number of patients with end-stage heart failure (HF) has been increasing over time. A left ventricular assist device (LVAD) implantation has been preferred more frequently for the treatment of medical therapy-resistant end-stage HF patients, owing to improved success rates over the last three decades.[1] The Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) study showed that patients receiving LVAD for end-stage HF had two-fold one-year survival rates, compared to those receiving optimal medical therapy.[2] These devices are frequently used to bridge-to-transplantation for end stage HF and, as outcomes are promoted with the improvements in patient care and technology, a trend toward destination therapy arises over the years for those who are ineligible for the transplantation.

End-stage HF is often associated with renal insufficiency. Additionally, factors such as high right atrial pressure, adverse neuroendocrine regulation, and high dose of diuretics contribute to renal failure.[3] Renal failure accompanied by HF (cardio-renal syndrome Type 2) is a mediator of worse outcome.[4] Given the fact that LVAD support has apparent cardiac therapeutic effects, preoperative renal status of the patient must be considered during the decision-making process prior to implantation.[5] Furthermore, the decision of post-LVAD treatment option (destination therapy or heart transplantation [HTx]) also depends on the patient's renal reserve, which guides our postoperative strategy.

In this study, we aimed to investigate the mid-term effects of LVAD therapy on kidney functions in end-stage HF patients.

PATIENTS AND METHODS

Between January 2015 and December 2017, a total of 87 patients with intractable end-stage HF underwent LVAD implantation at Kartal Kosuyolu Heart Training and Research Hospital. Twenty-six patients were excluded from the study due to a short duration of survival than six months or included in HTx before the postoperative six months. Finally, 61 patients (53 males, 8 females; mean age 46.4±11.2 years; range, 20 to 67 years) who received more than six-month LVAD support were included in this retrospective study. The study protocol was approved by the institutional Ethics Committee of Kartal Koşuyolu Yüksek İhtisas Training and Research Hospital. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Demographic data, left ventricular ejection fraction (LVEF), type of LVAD implanted, preoperative use of inotropic agents, preoperative intra-aortic balloon pump (IABP) insertion, and perioperative laboratory test results were recorded. The glomerular filtration rate (GFR) which was calculated using the Modification of Diet in Renal Disease formula {eGFR (mL/min/1.73 m^2) = 175 × [serum creatinine (mol/L) × 0.0113]-1.154 × age (years)-0.203 (× 0.742 if female)} was used to evaluate renal functions before and after surgery. According to the preoperative GFR values, the patients were divided into three groups: GFR ≤60 mL/min/1.73 m^2 (Group 1), GFR 61-90 mL/min/1.73 m^2 (Group 2), and GFR >90 mL/min/1.73 m^2 (Group 3). Renal functions after LVAD implantation were evaluated preoperatively and at 24 and 48 h, at one week, and at one, three, and six months postoperatively. Intra- and inter-group assessment was performed for postoperative course of renal insufficiency.

Statistical analysis

Statistical analysis was performed using the SPSS version 15.0 software (SPSS Inc., Chicago, IL, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max), interquartile range, or number and frequency. Continuous random variables were compared using the one-way analysis of variance (ANOVA) with the Tukey post-hoc test or Kruskal-Wallis ANOVA with the Dunn's post-hoc test between the groups according to the data distribution (normally or non-normally distributed), while intra-group analysis was performed using the repeated measures of ANOVA with the Tukey Kramer post-hoc test or Friedman test with the Dunn's post-hoc test. For the categorical random variables, the chi-square test was used. A new variable, namely percent of change, was calculated between the preoperative values and postoperative values at 24 and 48 h, at one week, and at one, three, and six months and, then, one-way ANOVA was used to compare these new variables between the groups. A p value of <0.05 was considered statistically significant.

RESULTS

Demographic data are shown in Table 1. The leading etiology of HF was dilated cardiomyopathy. Right ventricular functions were relatively preserved, despite impaired LV functions in all patients. More than two-thirds of the patients needed inotropic support preoperatively and IABP-support was applied for hemodynamic stabilization in six patients in Group 2 and eight patients in Group 3. All patients were under diuretic therapy without the need for renal replacement therapy (RRT) preoperatively. All patients following LVAD implantation needed inotropic support

Table 1. Demographic data of patients

	All patients (n=61)				Group 1 (n=8) (GFR ≤60)					Group 2 (n=21) (GFR 61-90)					Group 3 (n=32) (GFR >90)					
	n	%	Mean±SD	Range	n	%	Mean±SD	Median	Range	n	%	Mean±SD	Median	Range	n	%	Mean±SD	Median	Range	*p*
Age (year)			46.4±11.2	20-67			54.4±11.3		34-67			49.1±9.8		20-59			42.7±10.7		21-61	0.02*
Gender																				0.56
Male	53	86.9			6	75				20	95.2				27	84.4				
BMI (kg/m^2)			24.9±3.9	16.4-38.8			23.2±3.3		16.4-26.8			25.2±3.4		19-36.9			25.1±4.3		17.6-38.8	0.41
Etiology (ischemic CMP)	33	54.1			3	37.5				15	71.4				15	46.9				0.13
LVEF (%)			18.7±3.4	15-25			18.1±2.6		15-20			19.5±3.5		15-25			18.3±3.5		15-25	0.38
CI (L/min/m^2)			1.6±0.3	1-2.3			1.6±0.3		1.2-2.1			1.64±0.3		1.2-2.2			1.6±0.3		1-2.3	0.85
CO (L/min)			3.1±0.7	2-5			3±0.8		2.2-4.8			3.14±0.7		2.1-5			3.04±0.6		2-4	0.83
MBP (mmHg)			74.4±12.2	46-102			79±14.1		65-102			76.3±11.1		53-93			72±12.3		46-100	0.24
CVP (mmHg)			12.3±4.6	4-22			12.9±5.2		6-19			12.2±5.3		4-22			12.1±4		5-20	0.92
PAP (mmHg)			36.5±9.6	11-52			38±10		24-52			37.6±11.8		11-52			35.5±8		24-50	0.67
PVR (wood)			4.5±3.1	0.3-18			4.7±3.3		1.7-11			5±4		0.3-18			4.2±2.3		1.2-10	0.63
TAPSE (cm)			14.4±3.7	8-28			15.5±4.4		10-22			15.1±3		10-22			13.8±3.8		8-28	0.50
Albumine (≥3.5 mg/dL)			3.6±0.5	2.6-4.5			3.8±0.5		3.2-4.4			3.7±0.5		2.7-4.5			3.4±0.6		2.6-4.4	0.12
Glucose (≥130 mg/dL)			142±49.1	68-272			123.1±37.7		84-196			149.5±53.2		68-272			141.7±48.9		76-261	0.44
Sodium (≥135 mmol/L)			134.4±5	121-142			132±6.4		121-141			136.1±3.5		128-141			133.9±5.2		122-142	0.09
Potassium (≤5 mmol/L)			4.1±0.5	2.8-5.6			4.2±0.8		3.2-5.6			4.1±0.5		3.1-5			4±0.5		2.8-4.7	0.44
Hemoglobin (≥12 g/dL)			10.8±1.8	8.1-15.4			11.7±2.4		8.1-15			10.9±2		8.1-15.4			10.4±1.5		8.2-13.7	0.20
CRP (≤3 mg/L)			2.8±3	0.2-13.2			2.4±2.1		0.2-5.9			2.2±2.3		0.3-7.9			3.2±3.5		0.2-13.2	0.6
Bilirubin (≤1.2 mg/dL)			1.3±1	0.4-6.7			0.96±0.3		0.6-1.3			0.91±0.5		0.4-2.1			1.7±1.3		0.4-6.7	<0.001†
Creatinine (≤1.2 mg/dL)			0.9±0.3	0.4-1.7			1.3±0.3		0.9-1.7			1±0.2		0.5-1.3			0.7±0.1		0.4-0.9	<0.001‡
pH			7.4±0.1				7.5±0.1					7.4±0.0					7.4±0.1			0.80
Lactate (mmol/L)			1.7±0.8				1.8±0.8					1.8±0.8					1.7±0.8			0.80
Inotropic drug use	42	68.9			4	50				12	57.1				26	81.3				0.08
IABP use	14	22.9			0	0				6	28.6				8	25				0.24
CPB time (min)			92.1±43.9					91	70-220				79	47-106				77	47-273	0.45
LVAD																				0.95
Heartmate-2	12	19.7			2	25				3	14.3				7	21.9				
Heartware	23	37.7			3	37.5				8	38.1				12	37.5				
Heartmate-3	26	42.6			3	37.5				10	47.6				13	40.6				

SD: Standard deviation; BMI: Body mass index; CMP: Cardiomyopathy; LVEF: Left ventricular ejection fraction; CI: Cardiac index; CO: Cardiac output; MBP: Mean arterial pressure; CVP: Central venous pressure; PAP: Pulmonary artery pressure; PVR: Pulmonary vascular resistance; TAPSE: Tricuspid annular plane systolic excursion; CRP: C-reactive protein; IABP: Intra-aortic balloon pump; CPB: Cardiopulmonary bypass; LVAD: Left ventricular assist device; * Difference between Group 3 and Group 1; † Differences between Group 2 and Group 3; ‡ Differences between Group 3 and Groups 1 and 2.

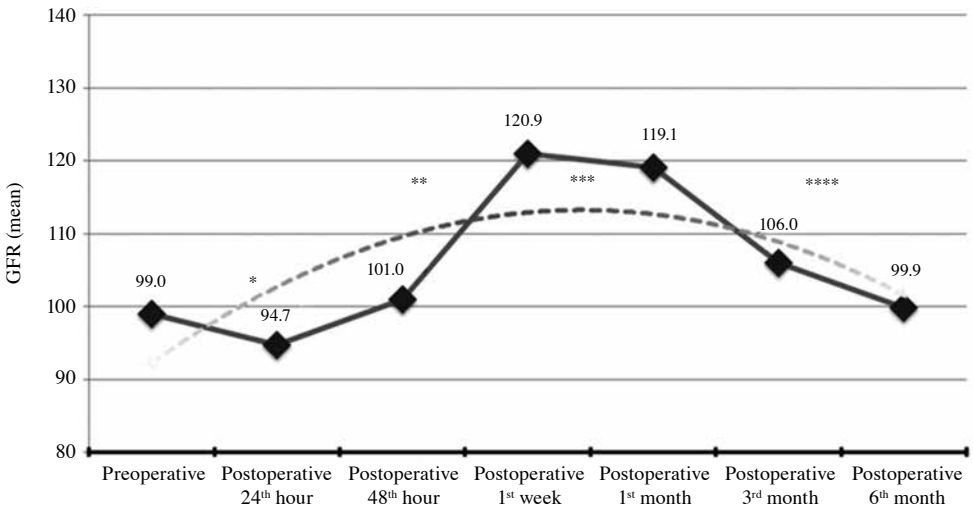


Figure 1. Glomerular filtration rate changes at specified time points after LVAD implantation.
GFR: Glomerular filtration rate; LVAD: Left ventricular assist device; * First change period (regression within the first 24 h); ** Second change period (progression after 48 h); *** Third change period (accession and stabilization between the first week and first month); **** Fourth change period (retrogression and retrocession after the first month)
Dash-line indicates alteration trend in postoperative GFR-response to LVAD within the first six months.

(mostly dobutamine and noradrenaline) with/without pulmonary vasodilator (nitric oxide and/or iloprost) and were under renal dopamine infusion. None of the patients needed IABP support. The main strategy was to maintain adequate cardiac output (CO) to prevent right heart failure and to avoid anemia, hypoalbuminemia, and hyponatremia. During the postoperative follow-up, seven patients (n=4 in Group 1 and n=3 in Group 3) developed reversible acute renal failure and required RRT. Two patients needed transient RRT and post-discharge kidney functions returned to normal. The other five patients required continuous RRT during their intensive care unit stay, and the causes of death were sepsis (n=2), cerebrovascular accident, device malfunction (n=1), and cardiac cirrhosis (n=1).

After LVAD implantation, statistically significant GFR changes were observed in the all groups at specific time points: *(i)* a statistically non-significant decrease was observed at the first day after LVAD implantation during the first change-period; *(ii)* a statistically

Table 2. Glomerular filtration rate changes at specified time points

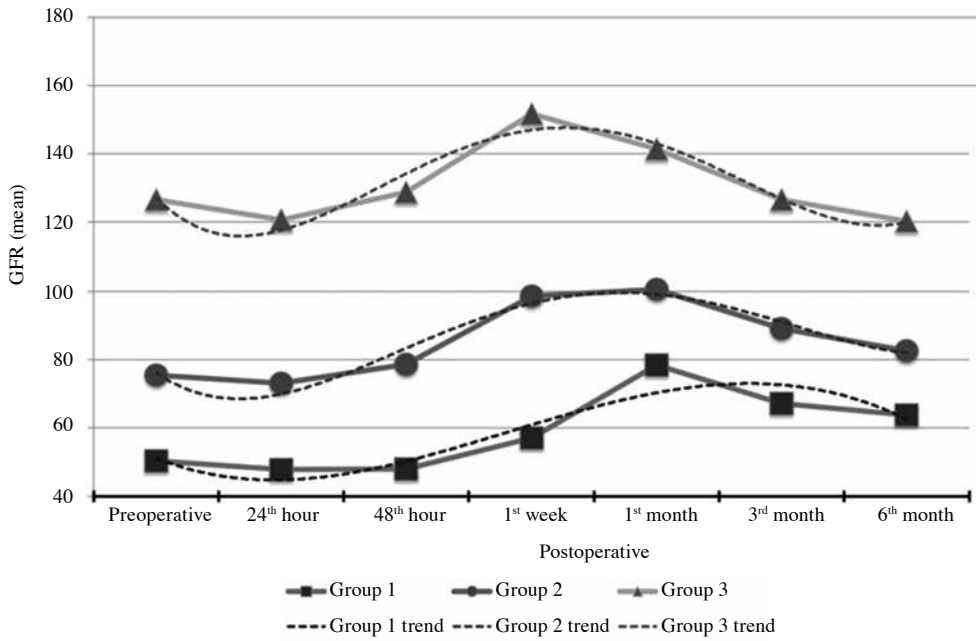
	Postoperative					
Comparison of GFR-levels between	24th hour 94.7±46.4 (22-256)	48th hour 101±54 (19-256)	1st week 120.9±56 (23-274)	1st month 119.1±42.5 (41-264)	3rd hour 106±34.3 (41-223)	6th month 99.9±30.8 (37-168)
	p	*p*	*p*	*p*	*p*	*p*
Preoperative 99±36.6 (39-198)	>0.05	>0.05	**<0.001**	**<0.01**	>0.05	>0.05
Postoperative						
24th hour 94.7±46.4 (22-256)		>0.05	**<0.001**	**<0.001**	>0.05	>0.05
48th hour 101±54 (19-256)			**<0.01**	**<0.01**	>0.05	>0.05
1st week 120.9±56 (23-274)				>0.05	>0.05	**<0.001**
1st month 119.1±42.5 (41-264)					>0.05	**<0.001**
3rd hour 106±34.3 (41-223)						>0.05

GFR: Glomerular filtration rate. GFRs are given in mean ± standard deviation, post-hoc analysis was performed using Tukey-Kramer test.

significant increase progressed after the second postoperative day and reached the peak level at the first week during the second change-period; *(iii)* the third change-period was drawing a plateau in the improvement, until the first postoperative month; and *(iv)* an impairment followed by regression to preoperative levels was observed at six months during the fourth change-period (Figure 1).

The improvement in renal function showed a concave curve, indicating a significant rebound from a statistical improvement to the baseline level. Therefore, the increase in the postoperative mean GFRs at one week and one month showed a statistically significant improvement, compared to preoperative GFR values, whereas the decrease in the postoperative mean GFR at six months showed a statistically significant decline, compared to increased postoperative GFR values at one week and one month in the all groups (Table 2).

The comparison of subgroups showed several significant changes (Figure 2). The patients of all



	Preoperative	Postoperative					
		24th hour	48th hour	1st week	1st month	3rd month	6th month
Group 1							
Mean±SD	50.4±8.5	47.9±12.4	48±14.5	57±20.1	78.5±29.4	67.2±18.7	63.7±20.7
Min-Max	39-60	30-64	28-76	23-78	48-123	41-90	37-95
Change by mean value		-5%	-5%	13%	56%	33%	27%
Group 2							
Mean±SD	75.5±9.7	73.1±25.6	78.6±31.6	98.6±29.1	100.6±38.6	89.1±25.1	82.5±17.5
Min-Max	62-90	22-131	19-129	38-168	41-218	58-134	57-112
Change by mean value		-3%	4%	31%	33%	18%	9%
Group 3							
Mean±SD	126.6±27.3	120.6±46.1	128.8±55.7	151.6±55.4	141.4±34.1	126.7±27.7	120.3±23.8
Min-Max	91-198	44-256	36-256	52-274	92-264	81-223	81-168
Change by mean value		-5%	2%	20%	12%	0	-5%

Figure 2. Glomerular filtration rate changes at specified time points after LVAD implantation.

Group 1: GFR ≤60 mL/min; Group 2: GFR 61-90 mL/min; Group 3: GFR >90 mL/min; GFR: Glomerular filtration rate; LVAD: Left ventricular assist device; SD: Standard deviation; Min: Minimum; Max: Maximum.

Table 3. Glomerular filtration rate percent of change values at specified time points

	Group 1 (n=8) (GFR ≤60)		Group 2 (n=21) (GFR 61-90)		Group 3 (n=32) (GFR >90)		
	Median	IQR	Median	IQR	Median	IQR	*p**
Preoperative							
24th hour	1.35	44.42	-12.33	42.69	-2.87	49.30	0.98
48th hour	-5.32	57.14	-3.12	49.44	3.11	62.24	0.96
1st week	4.24	50.72	24.14	26.58	16.36	42.27	0.65
Preoperative							
1st month	22.34	40.85	24.42	32.23	14.98	36.13	0.16
3rd month	22.80	38.26	16.09	35.99	-2.31	28.44	0.02†
6th month	11.47	91.38	13.33	28.03	-1.31	31.63	0.001‡

GFR: Glomerular filtration rate; IQR: Interquartile range; * Kruskal-Wallis test; † Difference between Group 3 and Group 1; ‡ Difference between Group 3 and Groups 1 and 2.

groups suffered from a slight decline in the mean postoperative GFR values immediately after surgery, particularly during the first 48 h. This time point was passed to stabilize the patients postoperatively, particularly to prevent bleeding and to adjust hemodynamic instability, intravascular volume reduction, and tissue hypoperfusion. Following the prospering management, a significant increase in the mean postoperative GFR was observed in all three groups during the first week postoperatively and achieved to peak levels in Groups 2 and 3 at one week and Group 1 at one month. As a consequence, the increase in the mean postoperative GFR began to decrease after reaching the peak level at one month in Group 1 and at one week in the Group 3. However, the increase in the mean postoperative GFR of Group 2 was reserved during the first postoperative month after reaching the peak level at one week and began to decrease afterwards. The first two groups had still higher mean GFR values at six months postoperatively, compared to preoperative levels and Group 3 showed a negative progress by impaired postoperative GFR values below the preoperative ones.

More interestingly, the first two groups continued to show an improvement until the sixth postoperative month, whereas Group 3 showed the very opposite case by reduction of postoperative GFR below the preoperative levels (Table 3). As a result, the first two groups showed a higher increase ratio in median percent of changes in GFR values between preoperative and at three months postoperatively (22.8% and 16.1%, respectively), compared to Group 3 (-2.3%). However, this decline back to baseline values in Group 3, reaching a statistical significance only in Group 1 at three months (p=0.02). The median and mean GFR values in Group 3 dropped below the preoperative levels at six months postoperatively. The median percent of change in GFR between preoperative and postoperative values at six months remained higher in Groups 1 and 2 (11.5% and 13.3%, respectively), compared to Group 3 (-1.3%). This decline reached a statistical significance in the other two groups (p=0.001).

DISCUSSION

In the present study, we evaluated the changes in renal function by calculating pre- and postoperative GFR values after LVAD implantation in the patients who suffered from end-stage HF with or without renal insufficiency, addressing into the effect of improvement in cardiac functions by LVAD on renal functions. A significant alteration wave in the postoperative GFR is the main finding of this study. An initial mild decrease in GFR at the first postoperative day was followed by a progressive and statistically significant increase during the first postoperative week. The improved GFR started to decline after the third postoperative month and to regress to the baseline values at the end of six months. The second finding is that temporary improvement of LVAD implantation on renal functions, irrespective of patients' demographic, clinical, and biochemical properties, varied according to preoperative GFR values. Group 1 including patients with the lowest preoperative GFR showed the most evident increase during the first postoperative month and had still a remarkable increase at six months. This was also observed in Group 2. The third and, maybe the most important result, is that patients without any preoperative renal damage were unable to get any benefit from the beneficial effect of LVAD

on renal functions. However, continuous arterial flow might have affected normo-functional kidneys adversely during mid-term follow-up.

Although many studies have indicated a significant improvement in renal functions and a considerable recovery in preoperative renal insufficiency in end-stage HF patients after LVAD implantation, a precise mechanism for this improvement has not been demonstrated.[6-9] Renal failure is the strongest indicator of postoperative mortality. Therefore, in patients with dialysis-dependent renal insufficiency or in patients with creatinine >5 mg/dL, mechanical support device implantation is relatively contraindicated, but mild and moderate renal disorders are improved by LVAD implantation.[10] This improvement in renal functions may develop in all patient groups after LVAD implantation, regardless of preoperative renal insufficiency degree.[11] Theoretically, an increase in CO after LVAD implantation is expected to improve renal perfusion and renal function.[12] This recovery usually occurs in the first month of LVAD implantation and remains stable for up to one year.[13,14] Despite positive mid-term benefits of LVAD implantation on renal functions, long-term effects of LVAD implantation (one to three years) is frustrating with regression of postoperative increased GFR values to preoperative values.[15,16] In addition, the degree of renal improvement after LVAD implantation is also related to preoperative GFR values. Several studies with subgroups formed by the severity of renal dysfunction showed that the worst subgroups with the lowest GFR values ended up with the most optimal renal improvement results after LVAD implantation.[12,14,17] It is reasonable to conclude that the cumulative effect of various mechanisms contributes to short-term renal improvement. The first mechanism may be the regulation of intra-renal hemodynamics after providing sufficient distal perfusion via balanced CO by LVAD support.[18] Secondly, the activity of the renin-angiotensin-aldosterone system (RAAS) diminishes within four to eight weeks after LVAD implantation.[19] Thirdly, sympathetic activity on the renal system becomes evident due to cardiopulmonary and aortic baroreceptor regulation, which results in decreased renal vascular resistance.[5,20] Finally, plasma epinephrine and norepinephrine levels reduce after LVAD implantation.[21]

The possible mechanism of GFR regression after LVAD implantation during long-term follow-up can be the hypertrophy of smooth muscles at renal arteries with an increase in collagen and decrease in elastin components in the aortic wall after long-term support by LVAD with the continuous flow.[22,23] This long-term, anti-physiological support causes severe periarteritis in kidneys and provokes the upregulation of RAAS in inflammatory cells due to loss of pulsatility in the systemic arterial circulation.[24] Another possible reason can be the development of renal tubular necrosis due to chronic hemolysis of blood components during long-term LVAD support. On the other hand, any right heart failure caused by elevated central venous pressure due to excessive left ventricle unloading or volume overload should not be ignored due to impairment of renal arterial circulation by renal venous congestion, i.e., inadequate renal perfusion and, consequently, deterioration in renal functions.[25]

In our study, a significant increase in GFR progressed after the second postoperative day in the all groups, and the highest peak level was reached at the first postoperative week. After reaching the peak level, this increase was stabilized until the first postoperative month; however, it could not be preserved and decline was started back to preoperative levels. However, postoperative GFR remained slightly elevated at six months and, in some, thereafter. The most interesting finding is that this negative reversal was most evident in Group 3, in which the mean postoperative GFR declined to the baseline level at three months postoperatively, earlier than the other two groups. Our study showed that the preoperative renal insufficiency degree was the only factor affecting the postoperative renal response. The regression of the improved GFR was limited in Groups 1 and 2, and this improvement still continued until the sixth postoperative month and, probably, thereafter. Only Group 3 showed a negative progress after the third postoperative month. The reason for this inverse wave movement may be the continuous arterial flow by LVADs, which affects renal cellular response adversely, and increased CO cannot further improve normal kidneys after surgery. However, we should keep in mind that the reduction of GFR in Group 3 does not exceed the preoperative GFR values. As the trend line of Group 3 indicates, the ideal period for HTx in this group may be the first month postoperatively. However, in this group of patients, there is no limited time for HTx due to the normal function of the kidneys. Group 2 patients with mild-to-moderate renal insufficiency showed a peak improvement at the first postoperative week and a durable improvement in GFR during the first postoperative month, which continued with a slight decline until the third postoperative month and, probably, thereafter. This group of patients suffered from inadequate renal perfusion due to lower CO preoperatively and benefits from balanced CO

by LVADs to provide further improvement in renal function postoperatively, particularly for the first three postoperative months. These patients may be treated first with LVADs to bridge to HTx with the goal of improvement in renal function before HTx and the reduction of adverse effects of immunosuppressive therapy on kidneys after HTx. As the trend line of Group 2 indicates, the ideal period for HTx in this group may spread within the first three months postoperatively. In our study, Group 1 patients with the lowest GFR preoperatively showed the highest improvement in GFR with a percentage of 56% at one month after LVAD support, which continued with a slight decline until the sixth postoperative month. This group of patients may have temporary or permanent primary or secondary kidney injury, and recovery probability of renal failure must be showed via balanced CO by LVAD to decide single or dual organ transplantation before HTx. As the trend line of Group 1 indicates, the ideal time for HTx in this group may begin after the first month and sustain until the sixth month postoperatively.

Currently, more end-stage HF patients expect HTx to hold on to life with LVAD therapy, and we hope that adverse effects of non-physiological circulation caused by LVADs can be improved with newly developed devices including physiological circulation dynamics. Perhaps the most promising aspect of these devices is that a significant improvement in preoperatively impaired renal function can make these patients more suitable for isolated HTx than dual (heart+kidney) transplantation. On the other hand, new devices with more kidney-protective effects may provide a new life chance for end-stage HF patients who are considered ineligible for HTx due to impaired renal functions.

The main limitation is the retrospective design of this study. Another limitation is that the number of patients evaluated for kidney function during follow-up was relatively low, as we were unable to include every lost patient or patients undergoing HTx before six months after LVAD implantation not to contort the analyses. The number of patients in each group limited our ability to distinguish differences among the groups and to investigate subgroup differences; however, most patients with impaired renal function was not included in HTx program and as well as LVAD program.

In conclusion, to benefit from left ventricular assist device implantation, optimization of the kidney-related outcomes of left ventricular assist device therapy should be tailored to the appropriate patient population by evaluating perioperative hemodynamic, physiological, pathological, and clinical characteristics. End-stage heart failure patients with preoperative renal insufficiency must be directed first to left ventricular assist device therapy to investigate any opportunity to be a candidate for isolated heart transplantation rather than for heart and renal transplantation, and additionally, to improve renal function before heart transplantation. Probably, it would be better to keep compensated end-stage heart failure patients with normo-function kidneys away from left ventricular assist device therapy until heart transplantation.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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