Original Paper

Biomarkers of Inflammation, Fibrosis, and Acute Kidney Injury in Patients with Heart Failure with and without Left Ventricular Assist Device Implantation

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Keywords

Left ventricular assist device · Biomarkers of fibrosis · Biomarkers of kidney injury · Inflammation

Abstract

Background/Aims: Renal dysfunction or renal failure is a common complication in left ventricular assist device (LVAD) recipients and is associated with reduced survival. To date, serum creatinine and glomerular filtration rate (GFR) are used for the evaluation of kidney function. However, serum creatinine and GFR have limitations. The objective of our study is to assess the levels of kidney biomarkers in LVAD recipients compared to heart failure patients and healthy controls and to examine their association with conventional clinical biomarkers. **Methods:** The biomarkers neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), plasminogen activator inhibitor-1 (PAI-1), and adiponectin were assessed in 51 participants: 19 heart failure patients, 16 LVAD recipients, and 16 healthy controls. Linear regressions were performed to assess whether demographic and clinical variables predict the levels of biomarkers that are associated with acute kidney injury and the risk of chronic kidney disease. **Results:** The levels of NGAL and adiponectin were higher in LVAD recipients and patients with heart failure as compared with healthy controls. The levels of PAI-1 and KIM-1 were

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not elevated in LVAD recipients. The results of linear regression analysis indicated that when controlling for the effect of CRP and BNP, 40.1% of the variance in NGAL levels can be explained by GFR ($R^2 = 0.401$, $F = 5.56$, $p = 0.005$), while CRP can explain 35.3% of the variance in adiponectin levels ($R^2 = 0.353$, $F = 4.55$, $p = 0.01$), when controlling for the effect of BNP and GFR. **Conclusions:** The levels of NGAL and adiponectin were augmented in LVAD recipients, suggesting that renal functions were not restored with circulatory support. Larger studies should assess the predictability of these biomarkers of renal dysfunction in LVAD recipients.

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Introduction

In heart failure patients, left ventricular assist device (LVAD) therapy improves cardiac output and organ perfusion [1]. In most patients with end-stage heart failure, renal function, assessed as glomerular filtration rate (GFR), significantly improved after LVAD implantation [2]. However, renal dysfunction is a common complication in LVAD recipients and is associated with reduced survival [3–5]. To date, serum creatinine and GFR are routinely used for the evaluation of kidney function. However, the early detection and accurate estimation of serum creatinine and GFR of renal injury in acute kidney injury (AKI) has limitations [6]. New biomarkers have been found to be associated with the risk of AKI, including neutrophil gelatinase-associated lipocalin (NGAL) [7, 8] and kidney injury molecule-1 (KIM-1), [9], while plasminogen activator inhibitor-1 (PAI-1) [10] and adiponectin [11] are associated with the risk of chronic kidney disease (CKD).

Very few studies have assessed the levels of these relatively new biomarkers in LVAD recipients and their association with the conventional kidney assessment methods such as GFR and creatinine. A previous study found that perioperative measurement of plasma NGAL levels predicted severe AKI, a requirement for renal replacement therapy, and renal recovery in LVAD recipients [12]. Another study found that NGAL levels remain abnormal from pre- to post-LVAD implantation, despite the concomitant decrease in creatinine, suggesting that some aspects of renal dysfunction are not fully detected with the conventional clinical measures [13]. In fact, many LVAD patients experience renal dysfunction due to chronic cardiorenal syndrome [14]. This hemodynamic-renal disorder should often be normalized following LVAD implantation [15]. However, we hypothesize that there exists residual hemodynamic renal disease that may be related to the lack of pulsatility of the continuous-flow LVAD support that prevents long-term normalization of kidney functions.

Very limited data are available for KIM-1 and PAI-1 in LVAD recipients. The objective of our study is to assess the levels of kidney biomarkers in LVAD recipients compared to heart failure patients and healthy controls and to examine their association with conventional clinical biomarkers (creatinine and GFR).

Methods

Levels of NGAL, adiponectin, KIM-1, and PAI-1 were measured in a cohort of LVAD recipients, patients with heart failure, and healthy controls.

Subjects

In total, 51 participants were included in the study: 19 heart failure patients, 16 LVAD recipients, and 16 healthy controls. LVAD recipients and heart failure patients were recruited from the Heart Function Clinic at Toronto General Hospital (Toronto, ON, Canada), while healthy controls were recruited using posters

throughout the hospital. Medical history records were obtained from each of the study participants and clinical data were recorded. The LVAD recipients were supported by a continuous-flow device for at least 8 weeks either as a bridge to cardiac transplantation or as a destination therapy. Heart failure patients were NYHA Class IV and candidates for LVAD implantation. Exclusion criteria for LVAD recipients and heart failure patients were: (1) renal failure ($\text{GFR} < 30 \text{ mL/min/1.73 m}^2$), (2) recent thromboembolic event (within the last 3 months), (3) right ventricular failure or severe irreversible pulmonary hypertension (mean pulmonary artery pressure $> 55 \text{ mm Hg}$), (4) liver failure, and (5) active infection and inflammation (including percutaneous driveline infection). Healthy control individuals were free of any known disease, including cardiovascular disease, renal disease, and diabetes. Eligible study participants in all three groups were between 33 and 72 years of age.

Biomarker Analysis

Blood samples were obtained during the visit to the Heart Function Clinic following a 12-h fast and collected in chilled tubes containing ethylenediaminetetraacetic acid (EDTA). The samples were then immediately centrifuged at $2,056 g$ for 15 min at 4°C and the plasma was stored at -80°C until analysis. The multiplex assay was performed using the Bio-Plex™ 200 system (Bio-Rad Laboratories, Inc., Hercules, CA, USA) and Human Kidney Injury kit (Millipore, St. Charles, MO, USA) according to the manufacturer's protocol. The 3-Plex consisted of lipocalin-2/NGAL, PAI-1, and adiponectin. The 1-Plex consisted of KIM-1. The assay sensitivity for lipocalin-2, PAI-1, and adiponectin are 1.7, 4.1, and 11 pg/mL, respectively. The assay sensitivity for KIM-1 is 0.177 ng/mL. Plasma C-reactive protein (CRP) was measured by latex-enhanced nephelometry on a Siemens BN II nephelometer analyzer.

Statistical Analysis

All statistical analyses were performed using the statistical package SPSS (version 14.0). The differences between the levels of biomarkers were compared between the LVAD recipients, heart failure patients, and healthy controls. A 1-way or 2-way analysis of variance (ANOVA) was performed followed by Fisher's least significant difference post hoc analysis. For data sets that were not normally distributed, the Kruskal-Wallis analysis followed by the Mann-Whitney test with Bonferroni correction was performed to assess the differences. A univariate correlation analysis was performed, using the Spearman rank correlation coefficient between each biomarker's levels and age, BMI, CRP, GFR, and B-type natriuretic peptide (BNP). Those showing a significant correlation in the univariate analysis ($p < 0.05$) were fed into regression models. Multivariable logistic regression was performed to assess whether these variables significantly predict biomarkers that are associated with AKI and CKD. Data are presented as median and 25th and 75th percentiles and mean $\pm$ SD. A p value ≤ 0.05 was considered statistically significant.

Results

Patients' baseline characteristics are described in Table 1 and clinical data are presented in Table 2, respectively. No patients required dialysis or had adverse events at the time of blood collections. LVAD recipients did not have any adverse events related to their LVAD and the levels of LDH, a marker of hemolysis, were $306.5 \pm 48.9 \text{ U/L}$. The average age of the participants was 55.1 ± 9.4 years. The levels of NGAL were higher in patients with heart failure and LVAD recipients as compared with healthy controls. There were no differences between the levels of NGAL in LVAD recipients and patients with heart failure (Fig. 1a). The levels of PAI-1 were highest in patients with heart failure as compared with LVAD recipients and healthy controls. There were no differences between the levels of PAI-1 in LVAD recipients and healthy controls (Fig. 1b). The levels of KIM-1 were not significantly different among the groups (Fig. 1c). The levels of adiponectin were higher in patients with heart failure and LVAD recipients as compared with healthy controls. There were no differences between the levels of adiponectin in LVAD recipients and patients with heart failure (Fig. 1d).

Table 1. Characteristics of study participants

	Healthy controls (n = 16)	Heart failure (n = 19)	LVAD (n = 16)	p value
Weight, kg	73.7±14.3	84.2±21.0	74.6±16.2	0.5
Height, cm	168.3±10.9	172.4±11.8	170.8±11.5	0.1
BMI, kg/m ²	26.0±4.3	28.1±6.2	25.1±3.1	0.1
BNP, pg/mL	18.0±10.0	924.8±859.8	325.4±216.1	0.001 ^{†,‡}

[†] Significant differences between LVAD recipients and heart failure patients. [‡] Significant differences between heart failure patients and healthy controls.

Table 2. Clinical data of heart failure patients and LVAD recipients

Variables	Heart failure (n = 19)	LVAD (n = 16)	p value
Diagnosis			
Ischemic cardiomyopathy	37 (7)	33 (5)	–
Nonischemic cardiomyopathy	63 (12)	67 (13)	
GFR, mL/min/1.73 m ²	55.5±28.9	65.6±25.0	0.27
Creatinine, Umol/L	134.6±58.8	101.1±33.1	0.04*
CRP, mg/L	16.2±17.3	12.69±10.7	0.04*
Flow, L/min	–	4.3±0.65	–
Motor power, W	–	4.5±1.3	–
Pulsatility index	–	5.5±0.44	–
Speed, RPM	–	5,839.3±3,112.1	–
Sildenafil (60–120 mg)	15.7 (3)	25.0 (4)	–
Hydralazine (30–125 mg)	10.5 (2)	25.0% (4)	–
Aspirin (81–325 mg)	63.1 (12)	68.7 (11)	–
Warfarin (36.25 mg)	68.4 (13)	87.5 (14)	–
Aggrenox (25–200 mg)	0.0 (0)	6.2 (1)	–
Lasix	78.9 (15)	75.0 (12)	–
β-Blockers	63.1 (12)	68.7 (11)	–
ACE inhibitors	31.5 (6)	56.2 (9)	–
Angiotensin receptor blockers	15.7 (3)	6.2 (1)	–
Aldosterone antagonists	52.6 (10)	75.0 (12)	–
Proton pump inhibitor	21.0 (4)	62.5 (10)	–
Antiarrhythmic drug	36.8 (7)	43.7 (7)	–

Data are presented as % (n) or mean ± SD, as appropriate. * Significant differences between LVAD recipients and healthy controls.

Association of Kidney Function with Biomarker Levels

In LVAD recipients, the levels of NGAL, PAI-1, KIM-1, and adiponectin were not associated with pulsatility index, flow, motor power, speed, and length of LVAD support. Results of the univariate analysis revealed that PAI-1 and KIM-1 levels were not associated with age, BMI, CRP, and GFR in patients with heart failure or in LVAD recipients. Only PAI-1, but not KIM-1, was positively correlated ($r = 0.43$, $p = 0.004$) with the levels of BNP in these patients. NGAL levels in patients with heart failure and in LVAD recipients were negatively associated with GFR (Fig. 2a) and positively associated with age (Fig. 2b) and CRP levels ($r = 0.32$, $p = 0.02$), but not with BNP. Adiponectin levels in patients with heart failure and in LVAD recipients were positively correlated with CRP ($r = 0.48$, $p = 0.001$) and BNP ($r = 0.37$, $p = 0.008$).

Fig. 1. **a** NGAL levels in LVAD recipients, heart failure patients, and healthy controls. **b** PAI-1 levels in LVAD recipients, heart failure patients, and healthy controls. **c** KIM-1 levels in LVAD recipients, heart failure patients, and healthy controls. **d** Adiponectin levels in LVAD recipients, heart failure patients, and healthy controls.

Fig. 2. **a** Association of NGAL with creatinine levels and GFR in patients with heart failure and in LVAD recipients. **b** Association of NGAL levels with age in patients with heart failure and in LVAD recipients.

Table 3. Multivariable regression results of NGAL and adiponectin in heart failure patients and LVAD recipients

	Unstandardized β-coefficient	Standardized β-coefficient	t value	p value	95% CI
NGAL					
GFR	−0.66	−0.53	−3.42	0.002*	−1.07 to −0.26
CRP	0.69	0.30	1.93	0.06	−0.04 to 1.43
BNP	−0.01	−0.29	−1.91	0.06	−0.03 to 0.001
Adiponectin					
GFR	−214.5	−0.16	−1.01	0.32	−651.8 to 222.6
CRP	1,270.6	0.55	3.40	0.002*	502.1 to 2,039.0
BNP	11.0	0.20	1.27	0.21	−6.8 to 28.9

* Significant differences between LVAD recipients and healthy controls.

Results of the multivariable logistic regression analysis indicated that GFR levels were negatively associated with NGAL levels, whereas there were trends of association between NGAL levels and CRP and BNP (Table 3). When controlling for the effect of CRP and BNP, 40.1% of the variance in NGAL levels can be explained by GFR ($R^2 = 0.401$, $F = 5.56$, $p = 0.005$), while CRP and BNP were no longer associated with NGAL levels. The results of linear regression analysis indicated that CRP can explain 35.3% of the variance in adiponectin levels ($R^2 = 0.353$, $F = 4.55$, $p = 0.01$) when controlling for the effect of BNP and GFR. The levels of BNP and GFR were not associated with adiponectin levels.

Discussion

The findings of our study suggest that levels of NGAL and adiponectin were augmented in LVAD recipients and were similar to those of patients with heart failure. KIM-1 and PAI-1 levels in LVAD recipients were similar to those of the healthy controls.

During the initial period of continuous-flow LVAD use, concerns were raised regarding the effect of low pulsatile blood flow on end organ perfusion and function. However, studies have reported that both continuous-flow LVADs and pulsatile-flow LVADs provided sufficient blood flow to maintain adequate end-organ function during prolonged circulatory support, and that albumin, blood urea nitrogen, creatinine, creatinine clearance, and total bilirubin either improved or stayed within the normal range in both groups [16, 17]. Furthermore, in continuous-flow LVAD recipients, renal function improved following implantation and was associated with improved survival [18]. A previous study showed that continuous-flow LVAD support improves or maintains renal functions in the majority of heart failure patients [16]. However, in the LVAD literature, renal dysfunction is commonly defined as an estimated GFR (eGFR) <60 mL/min/1.73 m² [19]. LVAD recipients with renal dysfunction prior to implantation had poorer clinical outcomes (GFR <60 mL/min/1.73 m²) [20] and creatinine levels >1.96 mg/dL [21]. In most patients with end-stage heart failure, renal function, assessed as GFR [2] or creatinine [22], significantly improves after LVAD implantation.

However, the early detection and accurate estimation of serum creatinine and GFR in AKI has limitations [6]. Moreover, renal dysfunction or renal failure is a common complication in LVAD recipients and is associated with reduced survival [3–5]. In patients with heart failure

and in LVAD recipients, elevated NGAL levels were moderately negatively associated with GFR. A study that investigated NGAL levels from pre- to post-LVAD implantation found that these levels remain abnormal [13]. There were no differences in NGAL levels between patients with improvement and nonimprovement in an NT-pro BNP profile. Similarly, we did not find a significant association between BNP levels and NGAL in our patients. Studies reported that in the first hours after cardiopulmonary bypass [7] and coronary artery bypass graft, plasma NGAL was predictive of renal injury [8]. However, the clinical use of NGAL is limited due to diagnostic inaccuracy and the fact that it increases not only during AKI and CKD, but also during other chronic and acute conditions, such as inflammatory conditions, including sepsis, urinary tract infection, and obstructive pulmonary disease [23].

Adiponectin levels were elevated in patients with LVADs to a similar extent as in the healthy control individuals. We also found that elevated levels of adiponectin were positively associated with CRP levels in patients with heart failure and in LVAD recipients. Studies have shown that in patients with established CKD, the levels of adiponectin are abnormally high and predict progression of disease [11, 24]. High adiponectin levels were also associated with increased mortality in this cohort of patients with CKD [25]. In our study, KIM-1 levels were not significantly different among the groups. Although KIM-1 is a new, promising marker of kidney damage [26], some studies reported that KIM-1 levels are associated with glomerular filtration, but not with other urinary tubular damage markers [27, 28], and that the levels of KIM-1 differentiated poorly between patients with good or poor outcomes [28]. Other studies found that KIM-1 predicted the progression of kidney damage [29] or AKI in patients who underwent cardiac surgery [30]. We did not find differences between LVAD recipients and healthy control individuals. PAI-1, which plays a role in both thrombosis and fibrosis, is undetectable in normal kidneys, whereas plasma PAI-1 levels increase in CKD [10]. However, in a systematic review and meta-analysis, the highest quantile of blood PAI-1 level was associated with high coronary heart disease risk; therefore, this marker may not be a specific marker for kidney disease [31].

The limitations of this study include the small sample size, which did not allow for a more thorough multivariable analysis of variables that may have an effect on the levels of the kidney biomarkers. In addition, a longitudinal study to investigate the value of kidney biomarkers in the prediction of adverse outcomes, such as kidney failure and mortality, is important.

In conclusion, early detection of impaired renal function in LVAD recipients is important in order to treat these complex patients. Therefore, confirmation of the clinical utility of new biomarkers that allow early diagnosis of impaired renal function will allow for early management of these patients. We found that levels of NGAL and adiponectin were augmented in LVAD recipients and were similar to those of patients with heart failure, suggesting that renal functions were not restored with circulatory support. However, our results should be interpreted with caution, since inflammation was reported to be elevated in patients with LVADs [32, 33], which may account for the elevation in NGAL or adiponectin. In addition, larger studies should assess the predictability of these biomarkers of renal dysfunction in LVAD recipients.

Statement of Ethics

The study protocol was reviewed and approved by the University Health Network (UHN) Ethical Review Board. The research study was conducted in accordance with the World Medical Association Declaration of Helsinki. Informed consent was obtained from each patient prior to participating in the study.

Disclosure Statement

Dr. Vivek Rao is a consultant to CorMatrix and HeartWare. The other authors have no conflicts of interest to disclose.

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