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The Journal of Heart and Lung Transplantation

http://www.jhltonline.org

Association of pre-operative interleukin-6 levels with Interagency Registry for Mechanically Assisted Circulatory Support profiles and intensive care unit stay in left ventricular assist device patients

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KEYWORDS:
End-stage heart failure;
cytokines;
LVAD;
osteopontin;
INTERMACS

BACKGROUND: Inflammatory mechanisms are associated with worse prognosis in end-stage heart failure (ESHF) patients who require left ventricular assist device (LVAD) support. Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profiles describe patient condition at pre-implant and outcome. This study assessed the relationship among inflammation patterns and INTERMACS profiles in LVAD recipients.

METHOD: Thirty ESHF patients undergoing LVAD implantation as bridge to transplant were enrolled. Blood and urine samples were collected pre-operatively and serially up to 2 weeks post-operatively for assessment of inflammatory markers (plasma levels of interleukin [IL]-6, IL-8, IL-10, and osteopontin, a cardiac inflammatory-remodeling marker; and the urine neopterin/creatinine ratio, a monocyte activation marker). Multiorgan function was evaluated by the total sequential organ failure assessment (tSOFA) score. Outcomes of interest were early survival, post-LVAD tSOFA score, and intensive care unit (ICU) length of stay.

RESULTS: Fifteen patients had INTERMACS profiles 1 or 2 (Group A), and 15 had profiles 3 or 4 (Group B). At pre-implant, only IL-6 levels and the IL-6/IL-10 ratio were higher in Group A vs B. After LVAD implantation, neopterin/creatinine ratio and IL-8 levels increased more in Group A vs B. Osteopontin levels increased significantly only in Group B. The tSOFA score at 2 weeks post-LVAD and ICU duration were related with pre-implant IL-6 levels.

CONCLUSIONS: The INTERMACS profiles reflect the severity of the pre-operative inflammatory activation and the post-implant inflammatory response, affecting post-operative tSOFA score and ICU stay. Therefore, inflammation may contribute to poor outcome in patients with severe INTERMACS profile.

J Heart Lung Transplant 2012;31:625–33

Outcomes with implantable left ventricular assist devices (LVADs) have improved over time as a result of the technologic innovations of the devices and of increasing experience in patient selection and management.[1,2] The hazard for death remains highest during the early post-operative period, with a mortality of close to 20%.[3] A substantial portion of early deaths are due to pre-operative conditions, with patients undergoing implantation in a state of acute decompensation more prone to post-operative complications and poor outcome.

The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profiles have been specifically

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1053-2498/$ -see front matter
doi:10.1016/j.healun.2012.02.006

designed to describe the status of end-stage heart failure (ESHF) patients before mechanical circulatory support (MCS) and to classify advanced HF patients according to clinical condition and response to therapy.[4] When outcomes were assessed according to pre-operative INTERMACS profile, patients who were more stable at implant (INTERMACS profiles ≥ 3) had significantly better 6-month survival than unstable patients with acute decompensation (INTERMACS profiles 1 and 2),[5] supporting the concept that poor baseline hemodynamic status is associated with worse outcome after LVAD implantation.

Several studies have reported that the inflammatory milieu plays an important role in the development of early adverse events, such as multiorgan failure (MOF).[6,7] Elevated baseline concentrations of pro-inflammatory cytokines, such as interleukin (IL)-6, were found in patients who showed clinical deterioration after device implantation.[7] Moreover, an unbalanced inflammatory response after LVAD implantation, as evidenced by elevated IL-8 and IL-10 levels, plays an important role in the development of adverse events early after the operation.[6] Plasma levels of osteopontin (OPN), a phosphorylated acidic glycoprotein involved in extracellular matrix inflammatory modulation, were related to the severity of HF.[8] An experimental model showed OPN is abundantly produced by activated T cells and macrophages, and its levels are markedly increased in the failing LV myocardium, indicating a potential role of OPN in the inflammatory processes occurring in the heart of severely ill patients supported by MCS.

We hypothesize that acutely ill patients (INTERMACS profiles 1 and 2) have a worse pre-implant inflammatory milieu and that this status can affect the inflammatory response and the outcome after LVAD implantation. The purposes of this study were (1) to assess whether the INTERMACS profile was associated with different degrees of pre-implant inflammatory status, and (2) to evaluate the relationship between INTERMACS profile, post-operative inflammatory response, and early clinical outcome.

Material and methods

This study complied with the principles of the Declaration of Helsinki, and the study protocol was approved by the Niguarda Hospital Ethics Committee. All of the patients gave written informed consent to participate in the study.

Patients

Our study cohort consisted of 30 consecutive patients undergoing LVAD implantation as a bridge to transplant between January 2005 and March 2010 at the Cardiovascular Department of Niguarda Hospital. The peri-operative management protocol for LVAD recipients was substantially unchanged during these years. Twenty-nine patients received an axial continuous-flow device: 8 De Bakey LVADs (MicroMed Technology, Houston, TX), 6 Incor LVADs (Berlin Heart AG, Germany), and 15 HeartMate II LVADs (Thoratec, Pleasanton, CA) were implanted, and 1 pulsatile-flow pump (Novacor World Heart, Oakland, CA) was implanted.

The INTERMACS classification[4] at the time of implant was applied by agreement between cardiologists and cardiac surgeons: 9 patients were classified as INTERMACS profile 1, 6 as profile 2, 14 as profile 3, and only 1 patient as profile 4.

Study design and assays

Patients were divided in 2 groups: Group A included 15 hemodynamically unstable patients, despite optimized intensive medical therapy (INTERMACS profiles 1 and 2). Group B included 15 patients who were hemodynamically stable, although most required inotropic therapy (INTERMACS profiles 3 and 4).

Echocardiography was performed pre-operatively. Hemodynamic data were assessed pre-operatively and then daily, up to a maximum of 1 week, by means of a pulmonary artery Swan-Ganz catheter. Multiorgan function was monitored calculating the total Sequential Organ Failure Assessment (tSOFA) score.[9] The SOFA system is a daily score from 0 to 4 assigned in proportion to the severity of functional deterioration for each of 6 individual organ systems (cardiovascular, respiratory, hepatic, renal, neurologic, and hemocoagulative). The tSOFA score was calculated by adding the scores for each of the organ systems during the observation period.[6]

Right heart function was evaluated by considering right atrial pressure (RAP) together with the need for inotropic therapy. After the operation, right heart dysfunction was diagnosed in the presence of inotropic equivalent > 10 and/or RAP > 10 mm Hg.[10,11]

Inflammatory variables of plasma interleukin (IL)-6, IL-8, IL-10, and urine neopterin, a marker of monocyte activation, were measured pre-operatively and at 1, 7, and 14 days after LVAD implantation. Plasma OPN levels were additionally determined as a cardiac remodeling-associated inflammatory marker.

Inflammation and remodeling parameters

Plasma IL-6, IL-8, and IL-10 levels were measured according to the methods of the manufacturer of the enzyme-linked immunosorbent assays (R&D Systems, Minneapolis, MN), and plasma OPN was determined by a specific enzyme immunometric assays (TiterZyme EIA, Ann Arbor, MI). Urinary neopterin levels were measured by an isocratic high-performance liquid chromatography method as previously described[6] and were normalized by the urine creatinine concentrations and reported as neopterin/creatinine (Neo/Cr) ratio.

Statistical analysis

Data are expressed as median and interquartile range (first–third [IQR]) or frequency (percentage). Differences between groups were assessed by the non-parametric Mann-Whitney *U*-test or Kruskal-Wallis test for continuous variables and by the chi-square test or the Fisher exact test for categoric variables. Differences of time-course of biochemical variables between patient groups were assessed by the nonparametric Friedman test, followed by the Wilcoxon post-test. The association between outcomes and inflammatory variables was tested by Spearman's correlation test. Data were analyzed using SPSS 17.0 software (SPSS Inc, Chicago, IL). A two-tailed value of $p < 0.05$ was considered statistically significant.

Results

Pre-operative clinical findings and inflammation markers in LVAD recipients

The baseline characteristics of LVAD recipients are described in Table 1. Age, etiology of cardiac disease, LV impairment, as evaluated by echocardiographic measurements, and hemodynamic data were comparable between groups, as were N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) levels. Besides routine therapy for chronic HF (angiotensin-converting enzyme inhibitors, β-blockers, and diuretics), patients who were candidates for LVAD implantation in Group A had more inotropic support compared with Group B. The tSOFA score was significantly higher in Group A than in Group B.

Only plasma IL-6 levels were higher in Group A with respect to Group B (Table 1), with the highest values in patients with INTERMACS profile 1 (Figure 1). The IL-6–to–IL-10 level ratio ([IL-6/IL-10] ratio) was higher in Group A (Figure 2).

Table 1 Patient Characteristics

Variable[a]	Group A (n = 15)	Group B (n = 15)	p-value
Age, years	54 (41–61)	51 (47–63)	0.713
Male sex	14 (93)	13 (87)	>0.99
Etiology			>0.99
IDC	9 (60)	10 (67)	
ICM	6 (40)	5 (33)	
Pre-implant data			
LVEF, %	20 (18–24)	22 (18–26)	0.624
LVEDV, ml	241 (186–351)	265 (166–321)	0.755
LVEDD, mm	71 (62–79)	69 (61–72)	0.425
CI, liters/min/m^2	1.7 (1.5–2.2)	1.7 (1.4–1.8)	0.914
PCWP, mm Hg	27 (15–31)	27 (22, 33)	0.436
RAP, mm Hg	6 (5–10)	6 (4–9)	0.539
Drug therapy			
ACE inhibitor + ATII	11 (73)	11 (73)	1.000
β-Blocker	3 (20)	14 (93)	<0.001
Statins	2 (13)	5 (33)	0.390
Diuretics	8 (35)	15 (100)	0.006
Inotropic therapy	14 (93)	7 (47)	0.014
Inotropic equivalent	9 (7–12)	0 (0–6)	0.006
tSOFA score	6 (5–7)	4 (2–5)	0.011
Laboratory values			
Creatinine, mg/dl	1.02 (0.67–1.48)	1.14 (0.89–1.60)	0.567
Total bilirubin, mg/dl	1.43 (0.62–3.16)	1.19 (0.60–1.75)	0.683
IL-6, pg/ml	24.6 (3.8–45.0)	9.8 (2.4–18.2)	0.033
IL-8, pg/ml	11.3 (5.8–16.3)	6.9 (5.1–8.9)	0.161
IL-10, pg/ml	0 (0–3.0)	3.8 (0–16.8)	0.089
Neo/Cr, μmol/mmol	0.395 (0.279–0.741)	0.355 (0.233–0.573)	0.377
OPN, ng/ml	57.7 (32.7–119.9)	52.2 (43.2–87.4)	0.845
NT-pro-BNP, pg/ml	834 (440–5564)	5026 (1674–6303)	0.118
Peri-operative data			
Surgery time, min	340 (275–390)	325 (270–430)	>0.99
CPB time, min	92 (75–104)	82 (75–100)	0.870
Device,			0.552
De Bakey	5 (33)	3 (20)	
Incor	3 (20)	3 (20)	
HeartMate II	6 (40)	9 (60)	
Novacor	1 (7)	. . .	

ACE, angiotensin converting enzyme inhibitor; ATII, angiotensin II receptor antagonists; CI, cardiac index; CPB, cardiopulmonary bypass; IDC, idiopathic dilated cardiomyopathy; ICM, ischemic cardiomyopathy; IL, interleukin; LVEDV, left ventricular end-diastolic volume; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; Neo/Cr, neopterin-to-creatinine levels ratio; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide; OPN, osteopontin; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; tSOFA, total Sequential Organ Failure Assessment.

[a]Continuous data are expressed as median and interquartile range (first, third), and categoric data as (percentage).

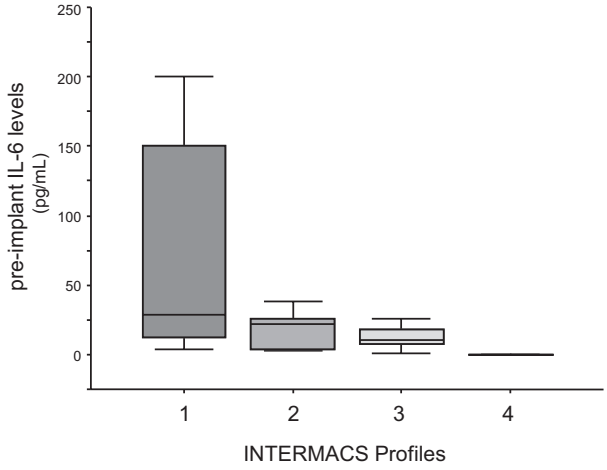

Figure 1 Pre-implant interleukin (IL)-6 levels are shown according to Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profiles of left ventricular assist device recipients. The horizontal line in the middle of each box indicates the median; the top and bottom borders of the box mark the 75th and 25th percentiles, respectively; and the whiskers represent the highest and lowest values that are not outliers or extreme values.

Hemodynamic and clinical course after LVAD implantation

After 1 week of MCS, hemodynamic improvement, as assessed by an increase of cardiac index (CI) and a decrease of pulmonary capillary wedge pressure (PCWP), was similar between the groups (Table 2). The tSOFA score increased, peaking at comparable values in both groups at 1 week after LVAD implantation (Figure 3). Both groups experienced comparable complications during the first month of LVAD support (Table 3).

Within 1 month after LVAD implantation, 5 of the 30 patients had died of MOF and 2 died of acute right HF

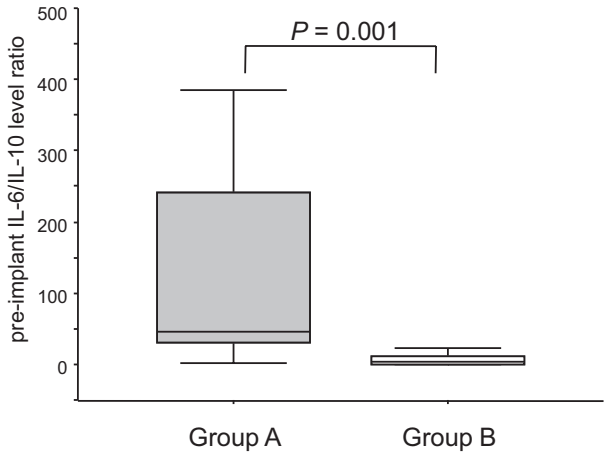

Figure 2 Pre-implant interleukin (IL)-6 to IL-10 level ratio is shown in Group A (dark box) and Group B (white box) patients. The horizontal line in the middle of each box indicates the median; the top and bottom borders of the box mark the 75th and 25th percentiles, respectively; and the whiskers represent the highest and lowest values that are not outliers or extreme values.

Table 2 Hemodynamic Parameters After 1 Week After Left Ventricular Assist Device

Variable[a]	Group A (n = 15)	Group B (n = 15)	p-value
CI, liters/min/m^2	2.9 (2.6–3.6)	3.2 (2.9–4.0)	0.381
PCWP, mmHg	11 (9–14)	9 (8–13)	0.340
RAP, mmHg	8 (6–9)	6 (4–9)	0.201

CI, cardiac index; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure.

[a]Data are expressed as median and interquartile range (first–third).

secondary to bilateral pneumonia. Early (1-month) mortality was similar between groups: 3 of 15 in Group A (20%) and 4 of 15 (27%) in Group B ($p > 0.99$). Among survivors, the median intensive care unit (ICU) length of stay was 14 days (IQR 11–20 days) and comparable between groups: 14 (10–25) days in Group A vs 11 (11–17) days in Group B ($p = 0.267$).

Post-LVAD inflammatory biomarker profiles

Plasma IL-6 and IL-10 levels increased after LVAD implantation (Figure 4), peaking at 24 hours after the operation at values significantly higher than baseline and comparable between groups (Figure 4A, B). IL-6/IL-10 ratios were also similar between groups (10.7 [IQR, 5.5–16.8] in Group A and 9.8 [3.1–15.8] in Group B at 24 hours post-LVAD; $p = 0.533$). Levels of neopterin/creatinine and IL-8 progres-

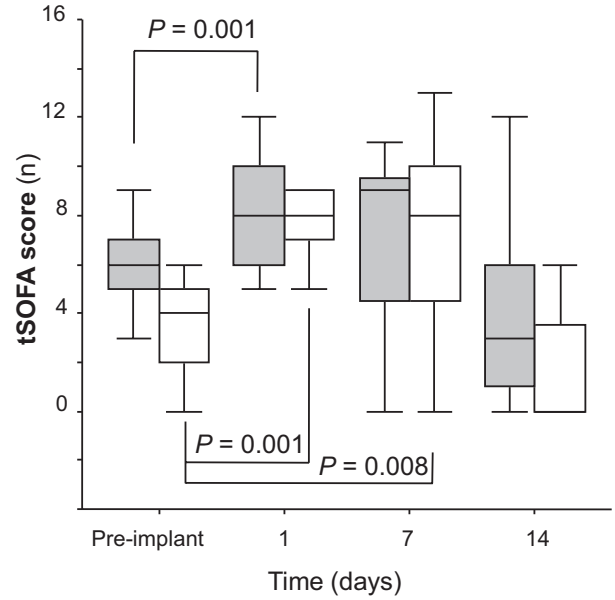

Figure 3 Panel time course of the total Sequential Organ Failure Assessment (tSOFA) score is shown after left ventricular assist device implant in Group A (gray boxes) and Group B (white boxes) patients. The horizontal line in the middle of each box indicates the median; the top and bottom borders of the box mark the 75th and 25th percentiles, respectively; and the whiskers represent the highest and lowest values that are not outliers or extreme values. The p-values are for differences with baseline for each group.

Table 3 Complications and Adverse Events During First Month of Left Ventricular Assist Device Support

Variables[a]	All patients ($n = 30$)	Group A ($n = 15$)	Group B ($n = 15$)	p-value A vs B
Bleeding				
Requiring surgery	1 (3)	—	1 (7)	>0.99
Requiring > 2 PRBC units	25 (83)	13 (87)	12 (80)	>0.99
Hemorrhagic	9 (30)	6 (40)	3 (20)	0.427
Embolism	1 (3)	1 (7)	—	>0.99
Arrhythmias				
Atrial	8 (27)	2 (13)	6 (40)	0.215
Ventricular	5 (17)	4 (27)	1 (7)	0.329
Ventricular tachycardia	3 (10)	3 (20)	—	0.224
Infection				
Sepsis	1 (3)	—	1 (7)	>0.99
Local non–device-related	3 (10)	2 (13)	1 (7)	>0.99
SIRS	3 (10)	2 (13)	1 (7)	>0.99
Respiratory failure	13 (43)	9 (60)	4 (27)	0.139
Renal failure	24 (80)	12 (80)	12 (80)	>0.99
Hepatic dysfunction	25 (83)	12 (83)	13 (87)	>0.99
Right heart failure	19 (63)	10 (67)	9 (60)	>0.99
Transient ischemic attack	1 (3)	1 (7)	—	>0.99
Psychologic	6 (20)	3 (20)	3 (20)	>0.99
Other neurologic	2 (7)	1 (7)	1 (7)	>0.99

PRBC, packed red blood cells; SIRS, systemic inflammatory response syndrome.
[a]Data are expressed as number (percentage).

sively increased during LVAD support in both groups (Figure 4C, D); however, IL-8 and neopterin/creatinine levels increased more in Group A than in Group B, with neopterin/creatinine levels at 14 post-LVAD days higher in Group A than in Group B ($p = 0.035$). Plasma OPN levels increased progressively during MCS only in Group B (Group A, $p = 0.272$ for time; Group B, $p = 0.014$ for time; Figure 5).

Relationships between biomarkers and outcomes

Only pre-implant IL-6 levels were positively correlated with the tSOFA score, both assessed before implant ($R = 0.60$, $p < 0.001$) and at 2 weeks after LVAD ($R = 0.53$, $p = 0.007$). Likewise, ICU stay was positively correlated with pre-implant IL-6 levels ($R = 0.60$, $p = 0.001$) and also with urinary neopterin/creatinine levels assessed at 1 and 2 weeks post-operatively ($R = 0.43$, $p = 0.022$, and $R = 0.68$, $p < 0.001$, respectively).

When patient data were examined according to tertiles of pre-implant IL-6 levels, LVAD patients with pre-implant IL-6 levels in the highest tertile (38.5 (IQR, 27.4–175.1] pg/ml) showed a more prolonged ICU length stay (Figure 6A) and higher tSOFA score at 2 weeks after LVAD (Figure 6B) compared with patients categorized within the lowest tertile of IL-6 (3.2 [IQR, 0.9–4.7] pg/ml). Patients who died were similarly distributed among the IL-6 levels tertiles (1 [10%], 3 [27%] and 3 [33%] not survived patients in the first, second, and third tertile of IL-6, respectively; $p = 0.451$).

Among biomarkers, plasma pre-implant IL-6 levels positively correlated with urinary neopterin/creatinine levels at 2 weeks after LVAD ($R = 0.61$, $p = 0.001$). Only plasma IL-8 levels assessed at 1 week after implant were higher in patients who died within 1 month than in survivors (29.2 (IQR, 26.9, 53.5] and 19.3 (15.9–36.5) pg/ml, respectively; $p = 0.037$).

Discussion

The findings from our study indicate that ESHF patients receiving long-term MCS and categorized by worst INTERMACS profiles are characterized before implant by more elevated IL-6 levels and IL-6/IL-10 ratios, and post-operatively, by a more pronounced IL-8 release and monocyte activation compared with patients with less severe INTERMACS profiles. LVAD patients with higher pre-implant IL-6 levels showed a more prolonged ICU stay and a greater worsening of multiorgan function in the early phase of MCS.

Pre-operative risk scores serve as a useful tool to accurately predict mortality and the probability of complications requiring special attention and management in ESHF patients receiving implantable LVADs. The INTERMACS profiles have offered a more precise categorization of the level of severity of illness than the traditional New York Heart Association classification in the setting of advanced HF. Patients in the most critical condition at implant, as categorized by INTERMACS classification, experienced worse survival than more stable patients,[12] with MOF as the main cause of death during the first month after device implantation.[13] Compared with patients with actual or im-

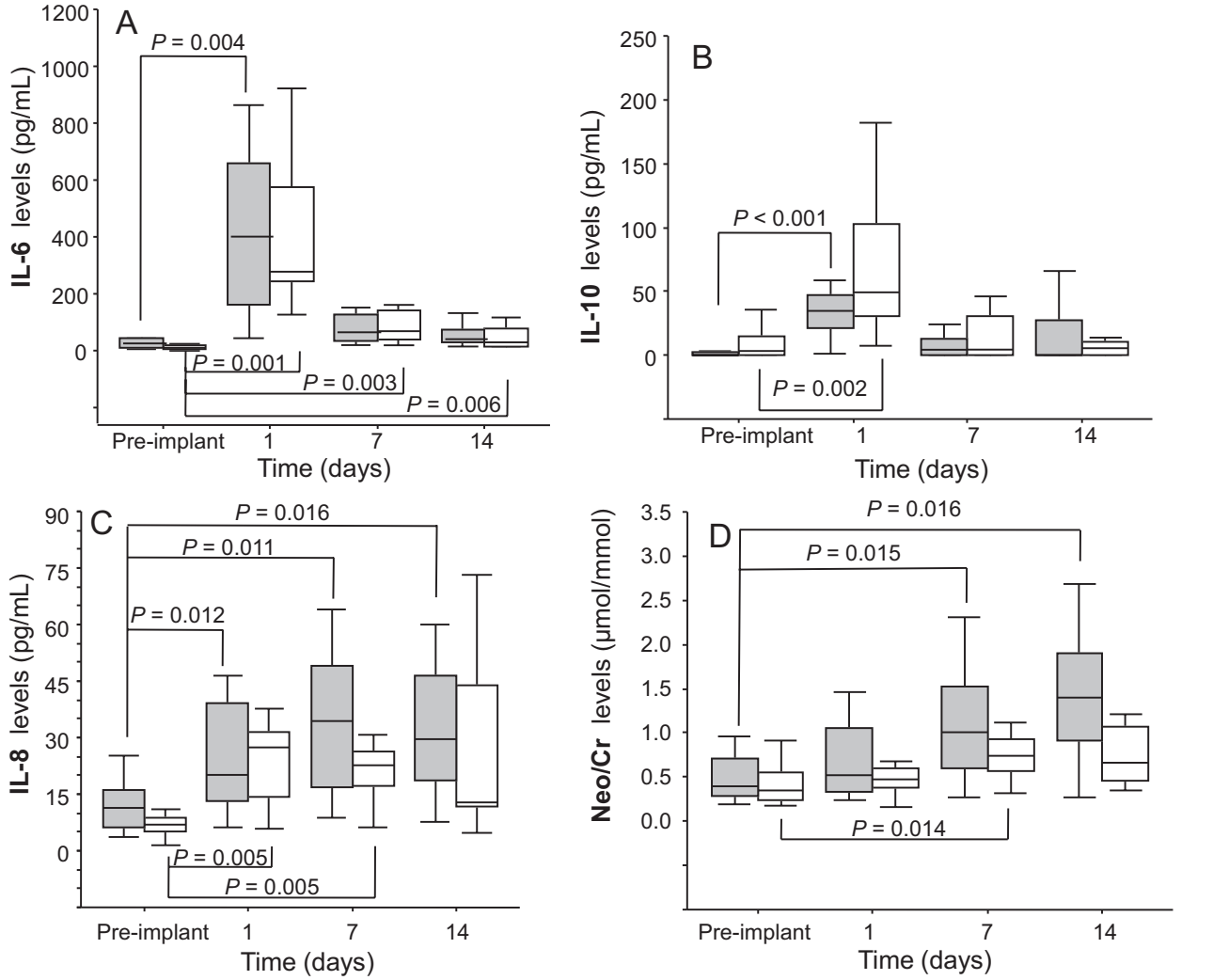

Figure 4 Time course of (A) plasma interleukin (IL)-6, (B) IL-10, (C) IL-8, and (D) urinary neopterin (Neo)/creatinine (Cr) is shown after left ventricular assist device (LVAD) implant in Group A (gray boxes) and Group B (white boxes) patients. The horizontal line in the middle of each box indicates the median; the top and bottom borders of the box mark the 75th and 25th percentiles, respectively; and the whiskers represent the highest and lowest values that are not outliers or extreme values. The *p*-values are for differences with baseline for each group.

pending cardiogenic shock, less sick patients had shorter hospital stay, greater survival to discharge, and a superior long-term survival rate.[5,14] In our cohort, the frequencies of early death and complications were comparable in groups characterized by different INTERMACS profiles, probably due to the limited population size. Nevertheless, Group A patients (INTERMACS profile 1 or 2) showed an unbalanced inflammatory status, with higher levels of IL-6 and lower levels of anti-inflammatory IL-10, as evidenced by higher IL-6/IL-10 ratio compared with patients with less severe INTERMACS profiles.

The IL-6 family cytokines, expressed in a wide variety of tissues and organs, are closely involved in the fine tuning of hypertrophic and apoptotic pathways of myocytes, representing signals of life and death, respectively, that modulate the evolution of HF.[15,16] Different values of peripheral IL-6 levels in our Group A and B patients cannot be attributed to differences in LV wall stress, because both groups showed similar echocardiographic parameters of LV and similar NT-pro-BNP levels. Furthermore, pre-implant plasma levels of OPN, which is expressed in the myocardium after LV pressure overload and HF development,[17] were similar in the 2 groups. A previous study reported that epinephrine administration in a porcine endotoxin shock model is associated with a marked effect on the IL-6 response of splanchnic reticuloendothelial tissues,[18] whereas another study observed that dopamine administration in chronic HF patients increased plasma IL-6 levels, suggesting that drugs modulating the sympathetic nervous system may alter IL-6 in these patients.[19] Moreover, in HF patients, prolonged reduced peripheral perfusion due to low cardiac output favors tissue hypoxia and degenerative changes of multiorgan function, with consequent production of pro-inflammatory cytokines.[20] Therefore the elevated IL-6 levels found in our patients categorized by INTERMACS profiles 1 and 2 may be partially imputed to inotropic therapy and to MOF, as expressed by higher tSOFA score.

In contrast to IL-6, IL-10 reduces both the duration and magnitude of the inflammatory process.[20,21] Therefore, the elevated IL-6 levels and IL-6/IL-10 ratio in patients with

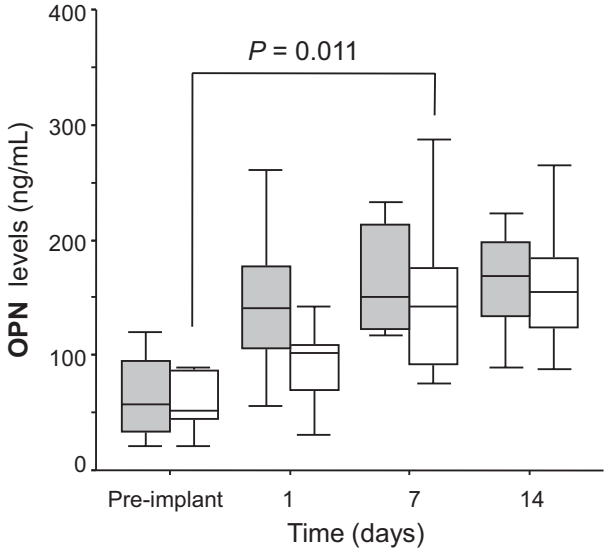

Figure 5 Time course of plasma osteopontin (OPN) levels is shown after left ventricular assist device implantation in Group A (gray boxes) and Group B (white boxes) patients. The horizontal line in the middle of each box indicates the median; the top and bottom borders of the box mark the 75th and 25th percentiles, respectively; and the whiskers represent the highest and lowest values that are not outliers or extreme values. The *p*-values are for differences with baseline for each group.

INTERMACS profiles 1 and 2 suggest that these patients are characterized by an over-activated and unbalanced inflammatory process compared with patients with less severe INTERMACS profiles. This pre-operative status may influence the post-operative inflammatory response and outcome. Indeed, patients with INTERMACS profiles 1 and 2 showed a more sustained increase of both IL-8 and neopterin levels. The pronounced post-operative increase of IL-8, a chemokine that attracts macrophages on endothelial cells, and of neopterin, a pteridine-derivative produced by activated monocytes, support the hypothesis that a more marked monocyte activation is implicated in the promoting inflammation following LVAD implantation in sickest patients, as evidenced also by the relationship between pre-implant IL-6 levels and neopterin/creatinine levels 2 weeks after operation. In spite of the differences in pre-implant IL-6 levels and IL-6/IL-10 ratios, Group A and B patients showed similar post-operative IL-6 and IL-10 kinetics, with similarly and elevated peaks at post-operative day 1. These data require elucidation with further investigations but underline the role of IL-6 levels at pre-implant on the severity of post-operative IL-8 response and monocyte activation.

The higher pre-implant levels of IL-6 and the more pronounced post-operative IL-8 expression and monocyte activation seem to be implicated, during the early phase on LVAD, both in maintaining an elevated tSOFA score, and in prolonging the ICU stay, reflecting a more critical clinical status during hospitalization. Indeed, pre-implant IL-6 levels correlated both to ICU length of stay and to the post-operative tSOFA score, as well to post-operative neopterin levels. Moreover, patients with higher pre-implant IL-6 levels were prone to more prolonged duration of ICU stay and severity of MOF at 2 weeks compared with LVAD recipients with lower pre-operative levels of IL-6. Higher levels of IL-8 at 1 week after implantation were found in non-surviving patients. These results are consistent with a previous report,[6] which included some of the patients of the present study, showing that LVAD patients who died because of MOF early after the operation had a marked increase of IL-8 levels during the first hours and days of device support, together with a progressive increase of neopterin levels.

These data suggest that the severity of hemodynamic instability of patients categorized by INTERMACS profiles 1 and 2 is associated with both an underlying unbalanced inflammatory milieu and a critical inflammatory response after LVAD implantation, which may exert an additional

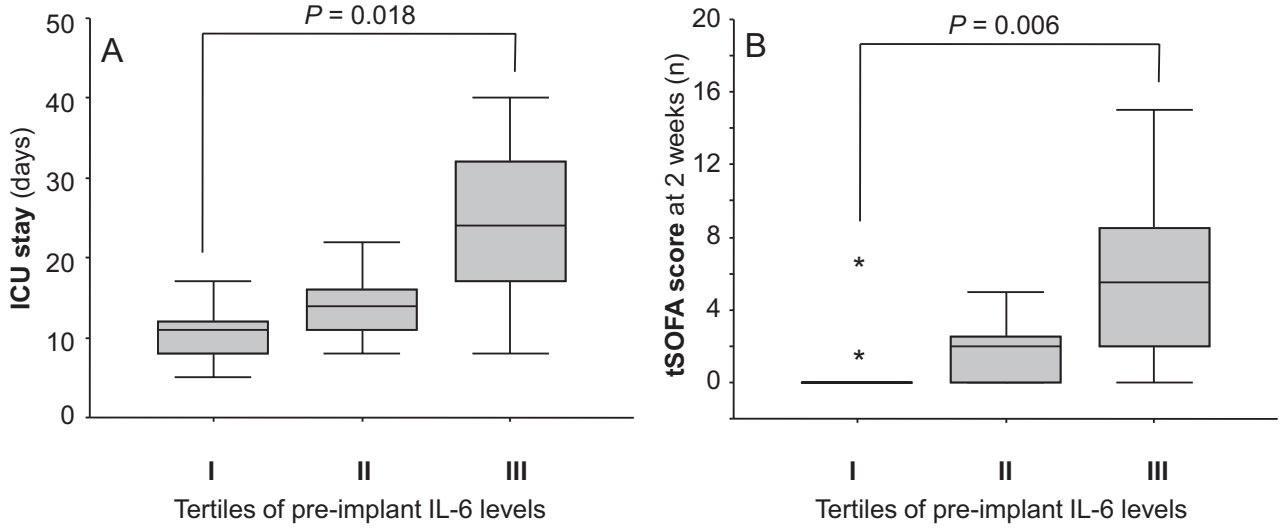

Figure 6 Length of (A) intensive care unit (ICU) stay and (B) the Sequential Organ Failure Assessment score at 2 weeks are shown (with the interquartile range [IQR]) according to tertiles of interleukin (IL)-6 levels at pre-implant. I, (first) tertile: 3.2 (0.93–4.7) pg/ml; II (second) tertile: 16.4 (10.6, 20.5) pg/ml; III (third) tertile: 37.9 (26.1–162.6) pg/ml. The *p*-values are vs I tertile by post-hoc test.

unfavorable effect on outcome, as observed in studies with larger populations,[12] and on the clinical course during hospitalization. Monocyte activation and expression of adhesion and chemotaxis molecules, involved in the cascade of leucocyte recruitment, are hallmarks of vascular inflammation, a common pathophysiologic response to diverse cardiovascular disease processes, and endothelial stunning in ICU patients.[22,23] Alterations of endothelial cell functions play an important role in MOF through capillary occlusion and altered perfusion induced by inflammation, immunity, and coagulation. The IL-6–dependent signals are proposed as crucial triggers in controlling monocyte activation and recruitment in vascular inflammation and endothelial dysfunction.[23] In the setting of ESHF patients who are candidates for LVAD, an upregulated IL-6 signalling pathway may represent the factor mediating post-operative systemic vascular inflammation, affecting multiorgan function and hospitalization. However, further work will be required to better understand the role of IL-6 in macrophage recruitment and activation in vascular complications of LVAD patients and to evaluate putative treatments targeted to contrast IL-6 signals and monocyte activation in the pre-implant or in the immediate post-operative phases.

In ESHF patients receiving a long-term LVAD support, plasma levels of OPN appeared to be modulated by LVAD, in agreement with a recent report.[24] Other studies reported that OPN modulates the cell biology of cardiac repair and plays a role in protecting against LV dilation after myocardial infarction and in modulating compensatory cardiac hypertrophy in response to chronic pressure overload.[24–26] In the phase of structural and functional remodeling, OPN may promote angiogenesis and extracellular matrix deposition.[24] In our study, during the first 2 weeks of mechanical support, the OPN levels increased more in LVAD patients with INTERMACS profiles 3 and 4 (ie, the less severely ill patients) than in patients with INTERMACS profiles 1 and 2, although a slightly trend to higher levels of OPN was observed in patients with the worst INTERMACS profiles in the first week. Therefore, the larger increment of plasma OPN levels found in Group B patients could conceivably represent a marker of better structural and functional response to unloading.

Although an increase of cardiac index and a decrease of LV filling pressure are more or less regularly observed in the first hours after LVAD implantation, end-organ function may improve or deteriorate in the early post-operative phase. True myocardial recovery is very uncommon in chronic HF patients, and when it occurs, it takes weeks to months to reach a level that allows LVAD removal. Inflammatory activation seems to play a role in dissociating tissue perfusion (and consequently end-organ function) from hemodynamic improvement in the early phase.

In conclusion, in ESHF patients needing long-term MCS, the INTERMACS profiles are associated with the severity of pre-operative inflammatory activation and post-implant inflammatory response. The lower degree of inflammatory response in patients with less severe INTERMACS profiles is also accompanied by a greater modulation of OPN, a potential marker of myocardial repair and recovery. Our study indicates that patients with elevated pre-implant IL-6 levels and more pronounced inflammatory post-operative response experienced a more complicated course during hospitalization, despite adequate hemodynamic improvement after LVAD implantation. Therefore, in patients with severe INTERMACS profiles, the pre-existing inflammation may contribute to worse outcome. Although our findings require validation in a larger patient population, combined evaluation of inflammatory mediators, in addition to clinical evaluation of LVAD candidates by INTERMACS profiles, appears to be a potential tool to ameliorate risk stratification and improve patient selection for LVAD implantation.

Disclosure statement

This study was partly supported by the FP7-ICT-2009 project grant agreement 24863 (SensorART—A Remote Controlled Sensorized ARTificial Heart Enabling Patients Empowerment and New Therapy Approaches), CNR National Project ME.01 Malattie Cardiopolmonari Department of Medicine, Fondazione Banca del Monte di Lombardia of Pavia, Italy, and Fondazione "A. De Gasperis" of Milan, Italy.

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript or other conflicts of interest to disclose.

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