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Review

New therapy, new challenges: The effects of long-term continuous flow left ventricular assist device on inflammation☆

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ABSTRACT

Surgically implanted continuous flow left ventricular assist devices (CF-LVADs) are currently used in patients with end-stage heart failure (HF). However, CF-LVAD therapy introduces a new set of complications and adverse events in these patients. Major adverse events with the CF-LVAD include right heart failure, vascular dysfunction, stroke, hepatic failure, and multi-organ failure, complications that may have inflammation as a common etiology. Our aim was to review the current evidence showing a relationship between these adverse events and elevated levels of inflammatory biomarkers in CF-LVAD recipients.

1. Introduction

Left ventricular assist devices (LVADs) have been developed to provide durable mechanical circulatory support in the setting of heart failure (HF) with reduced ejection fraction. The LVAD pump is implanted intrathoracically to provide sufficient blood flow to meet the metabolic demands of the body crucial for patient survival. Given the meaningful improvement in clinical outcomes seen with long-term support, the LVAD has become an established therapy for patients with end-stage HF as a bridge to transplantation [1,2], as a destination therapy [3] or 'bridge to recovery', in the last scenario allowing device removal without transplantation [4].

The first generation of LVADs was pulsatile in nature, with an internal reservoir chamber that functioned as an internal volume displacement pump, thereby mimicking the physiological function of the native heart [5]. However, the structural disadvantages and high mechanical failure rates of the pulsatile-flow (PF)-LVAD (PF-LVAD) have led to the development of continuous-flow LVADs (CF-LVADs) [6]. The newer generation CF-LVADs have been shown to confer some advantages over the PF-LVAD, including durability, smaller size, as well as a lower incidence of infections [6] and increased survival [7].

However, the effects of long-term, non-physiological, low-pulsatile blood flow of the CF-LVAD are not well understood [8]. Major adverse events with the CF-LVAD have included bleeding, thrombosis, ischemic and hemorrhagic strokes, renal impairment, multi-organ failure and infections, which have been the primary causes of death in some series [7,9–11]. The above-mentioned causes of morbidity and mortality have, at least in part, been attributed to the activation of inflammatory cascades [12–15] and to elevated levels of circulating neurohormones that are detrimental to the microvasculature of perfused tissues [12]. Thus, this new therapy for end-stage HF, CF-LVAD support, may predispose patients to a new set of complications and adverse events that requires new management considerations. Our aim was to review mechanisms responsible for the activation of inflammatory pathways as a consequence of LVAD support, as well as potential clinical consequences that result from increased levels of in inflammatory mediators in these patients.

2. Elevate levels of inflammation in LVAD support

2.1. Circulating inflammatory mediators during LVAD support

The effects of PF-LVAD on the levels of circulating inflammatory cytokines have been investigated in several studies. An early study reported that following PF-LVAD implantation, the cytokine interleukin 6 (IL-6) increased postoperatively, peaking on day 1 and remaining elevated during the first 20 post-operative days, while C-reactive protein (CRP) increased postoperatively, peaking on post-operative day 4 and remaining elevated during the first 25 postoperative days [16]. The investigators concluded that during the early postoperative

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period of LVAD implantation, the inflammatory response is pronounced and acute. An immediate increase in plasma cytokines IL-6 and IL-8 after implantation of PF-LVADs, followed by a decline after 6 weeks, has also been documented [17], reflecting systemic inflammatory effects following cardiovascular surgery. CRP levels have also been shown to be higher in patients bridging to cardiac transplantation by PF-LVAD and in patients awaiting cardiac transplantation on medical HF treatment compared to healthy controls, while PF-LVAD recipients had more pronounced inflammatory responses compared to HF patients on medical therapy [18]. Plasma tumor necrosis factor-α (TNF-α) levels have similarly been shown to be higher in HF patients treated with medical therapy than in healthy controls, with even further elevations seen in patients supported by PF-LVADs [19]. These findings may be due to the severity of HF symptoms in patients receiving PF-LVAD therapy. Alternatively, the device itself may contribute to the augmented levels of inflammation, possibly through the effect of blood contacting an artificial surface. Importantly, others have reported that following hemodynamic recovery after PF-LVAD implantation, the levels of serum cytokines IL-6 and IL-8 decreased compared to higher levels preoperatively, suggesting that alterations in systemic hemodynamics play a more prominent role compared to the effect of blood contact with the LVAD [20].

Another important consideration related to the interaction between hemodynamic function and inflammation is the comparison between devices that lead to continuous vs. pulsatile flow. Accordingly, a previous study comparing patients with CF-LVADs and PF-LVADs reported that all circulating inflammatory markers were elevated over a period of 3 months after implantation in both circulatory support devices, with no differences in TNF-α; however, levels of IL-6 were higher in CF-LVAD recipients than in patients with PF-LVAD support [21]. Similarly, circulating CRP levels were elevated with long-term CF-LVAD support, which was consistent with the increase in the levels of leukocytes [22]. In comparing patients with CF-LVAD, HF, and healthy controls, our group has shown that the inflammatory markers CRP, interferon gamma-induced protein-10 (IP-10), monocyte chemotactic protein-1 (MCP-1) and IL-8 levels were significantly higher to a similar level in both the CF-LVAD recipients and HF patients, compared to healthy controls, while granulocyte macrophage-colony stimulating factor (GM-CSF), macrophage inflammatory proteins-1β (MIP-1β) and macrophage-derived chemokine (MDC) were elevated more pronouncedly in CF-LVAD recipients compared with both HF and healthy control groups [23]. In a longitudinal study examining the long term effect of CF-LVAD, we found that despite improvements in left ventricular dimensions and BNP levels, MCP-1, IP-10, and CRP levels continue to remain elevated compared to pre-CF-LVAD implantation at 3, 6, and 9 months of CF-LVAD support, compared to healthy controls. Serum IL-8, TNF-α and MIP-β increased significantly at 9 months and MDC increased at 6 months post CF-LVAD implantation compared to the levels prior to CF-LVAD implantation [24]. In summary, CF-LVAD use is generally associated with higher levels of inflammatory markers compared to PF-LVAD users, patients with HF and also compared to healthy controls.

2.2. Inflammatory milieu in the cardiac tissue in LVAD recipients

Despite what is known about the role of inflammation based on circulating markers, few studies have investigated the inflammatory milieu in cardiac tissue obtained from CF-LVAD recipients (Table 1). Cardiac tissue studies have reported reduced myocardial TNF-α content in PF-LVAD recipients, with even greater reductions in patients who had been successfully weaned off pump support, due to cardiac recovery, compared to those who underwent transplantation [25]. The reduction in TNF-α levels was accompanied by a decrease in myocyte size and collagen content [26]. In addition to these changes in TNF-α levels, the activity of nuclear factor-kB, the transcription factor that regulates the genes for TNF-α and IL-6, was decreased in cardiomyocytes of HF patients following LVAD support [27]. Another study reported similar findings, in which IL-6 levels were significantly reduced in myocardial tissue following LVAD support, but in contrast found that inflammatory cytokines TNF-α remained elevated [28]. It is interesting to note that in a study comparing myocardium from patients with PF-LVAD and CF-LVAD support, TNF-α levels decreased to a similar extent [29].

Why are plasma levels of inflammatory biomarkers elevated while tissue levels are paradoxically suppressed? Although the answer to this question is currently not known, a recent investigation documented that IL-6 content in the myocardium collected at the time of implantation did not correlate with plasma levels of IL-6 levels or with the degree of severity of the clinical course, whereas plasma IL-6 and CRP concentrations did correlate with the length ICU stay, and with the total sequential organ failure assessment (tSOFA) score [30] (a mortality prediction score

Table 1
Inflammatory markers in LVAD recipients.

	Summary of findings	References
Inflammatory milieu in the cardiac tissue	↓ TNF-α content in myocardial tissue of PF-LVAD recipients.	Torre-Amione et al. (1999), Maybaum (2002)
	↓ TNF-α content in the myocardium in both CF-LVAD and PF-LVAD supports	Thohan et al. (2005)
	↓ NF-kB, the transcription factor, regulating genes for TNF-α and IL-6 in the cardiomyocytes (LVAD type was not specified).	Grabellus et al. (2002)
	↓ IL-6 and ↑ TNF-α gene expression in the myocardial tissue (LVAD type was not specified).	Bedi et al. (2008)
Circulating inflammatory markers	↑ IL-6 and CRP levels during early postoperative period in PF-LVAD implantation (peaking on day 1 and remaining elevated during the first 20–25 post-operative days)	Rothenburger et al. (2001)
	↑ Cytokines IL-6 and IL-8 levels after implantation of PF-LVADs, followed by a concentration decline after 6 weeks	Corry et al. (1998)
	↑ CRP levels was more pronounced in PF-LVAD recipients than HF patients on medical therapy.	Deng et al. (1999)
	↑ TNF-α levels were higher in patients supported by PF-LVADs than both HF patients and healthy control.	Bruggink et al. (2008)
	↓ IL-6 and IL-8 levels following hemodynamic recovery from the levels prior to PF-LVAD implantation.	Goldstein et al. (1997)
	↑ TNF-α, IL-1β, and IL-8 levels within hours to 7 days after post-implantation in non-survivors cohort of mainly CF-LVADs recipients.	Caruso et al. (2010)
	↑ Circulating inflammatory markers over a period of 3 months after implantation in CF-LVAD and PF-LVAD recipients. ↑ IL-6 levels were higher in CF-LVAD recipients than in patients with PF-LVAD support with no differences in TNF-α.	Loebe et al. (2001)
	↑ CRP levels were correlated with the levels of leukocytes in long-term CF-LVAD recipients	Thoennissen et al. (2006)
	↑CRP, IP-10, MCP-1 and IL-8 levels in CF-LVAD and HF failure groups compared to health controls, while ↑GM-CSF, MIP-1β and MDC more pronouncedly in CF-LVAD recipients compared with both HF and health controls groups.	Grosman-Rimon and Rao et al. (2014)
	↑ MCP-1, IP-10, and CRP levels continue to remain elevated from pre-CF-LVAD implantation at 3, 6, and 9 months of CF-LVAD support compared to health controls. ↑ IL-8, TNF-α and MIP-β ↑at 9 months and MDC increased at 6 months post CF-LVAD implantation compared to the levels prior to CF-LVAD implantation.	Grosman-Rimon and Rao et al. (2015)