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Procalcitonin and Other Inflammatory Measurements in Left-Ventricular Assist Device Recipients

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Abstract

Aim: Procalcitonin (PCT) has been identified as a marker of infection, but normal values in patients with a LVAD are not defined. The aim of our study was to define PCT levels in uninfected LVAD recipients, and to confirm prior studies reporting elevated inflammatory markers in LVAD recipients.

Method: White blood cell count (WBC), CRP, ESR and PCT were measured in 15 LVAD recipients.

Results: CRP (mean value 4.43 mg/L) and ESR (mean value 29.53 mm/hour) were elevated, but PCT levels were not (level<0.1 mcg/L in 14 patients, and 0.14 mcg/L in one patient).

Conclusion: Infections related to left-ventricular assist devices (LVAD) can be subtle. PCT may serve as a useful biomarker of infection in LVAD recipients.

Keywords: Procalcitonin; LVAD; Inflammation; Infections; Liver failure

Introduction

Left-ventricular assist devices (LVADs) are increasingly used as a bridge to heart transplantation and as long-term, destination therapy for patients unable to receive transplantation. Infection is a major complication, with rates ranging from 25% to 80% [1]. Examples of LVAD infections include, but are not limited to, local driveline exit site (DLES) infection, pocket infection, endovascular infection of cannulas or pump-hardware, and mediastinitis.

The diagnosis of LVAD-related infection can be challenging. DLES infection has been defined as an "infection involving the soft tissues surrounding the driveline exit site, typically accompanied by erythema, warmth, and purulent discharge" [1]. In practice, however, DLES infection may present more subtlety, with only increased drainage at the exit site and without local or systemic manifestations of infection. Similarly, pocket infections may present with a surprisingly indolent course. With both infections, WBC levels can be normal, blood cultures sterile and radiological studies complicated by the presence of artifacts caused by the metallic LVAD. The measurement of inflammatory levels as a marker of infection has been used as a diagnostic aide for some infections (such as osteomyelitis), but previous investigators have demonstrated that inflammatory levels (such as CRP) are normally elevated in uninfected LVAD recipients, thereby limiting their utility [2].

Procalcitonin (PCT) is the pro-hormone form of calcitonin, and extra-thyroidal immune cells produce it within 2 to 4 hours of a bacterial insult and/or inflammatory response. Elevated PCT has been observed in septic patients, and concentrations have correlated with the severity of disease [3]. Progressively increasing PCT is associated with a poor prognosis, while decreasing concentrations correlate to a good prognosis and/or a response to antibiotic therapy [4]. As a cut-off for the diagnosis of sepsis, plasma levels of >0.5 ng/mL are interpreted as abnormal and suggest sepsis [5]. The use PCT in as an aid in the diagnosis of LVAD-related infections has not been studied.

Methods

The study protocol was reviewed and approved by the Institutional Review Board at MedStar Washington Hospital Center, and all volunteers provided informed consent for study participation. LVAD recipients presenting for routine clinical follow-up were offered study participation. Volunteers were screened for study inclusion, and underwent a standardized evaluation for symptoms related to infection. Inclusion criteria were age greater than 18 years and the presence of a LVAD for at least 2 months. Exclusion criteria included severe renal impairment (creatinine clearance less than 30 mL/min/1.73 m^2), thromboembolic event within the past 3 months, right ventricular failure or severe irreversible pulmonary hypertension (mean pulmonary artery pressure>55 mmHg), liver failure, active infection, receipt of an antibiotic within the past 2 weeks, any surgical procedure within the past 2 months, or the receipt of any immunosuppressive medication. Volunteers who met study criteria underwent phlebotomy for PCT, ESR, CRP, and WBC. Volunteers were contacted two weeks after phlebotomy and questioned as to the development of any inter-current illnesses or receipt of antibiotics.

Statistical analysis

A sample size of 13 patients was estimated to provide 81% power to detect a difference of -0.9 between the null hypothesis mean of 0.1 and

the alternative hypothesis mean of 1. This had an estimated standard deviation of 1 and significance level (alpha) of 0.05 using a two-sided Wilcoxon test.

Results

Fifteen participants underwent phlebotomy and were included in final analysis. Mean age was 57.9 years (range: 41 to 72), 80% were male, and 93% were African-American (7% were Caucasian). The mean time from LVAD implantation to study entry was 15.9 months (range: 2 to 50). The mean WBC was 5.40 k/μL (range: 2.0 to 9.0), the mean ESR was 29.53 mm/hour (range: 9 to 71), and the mean CRP was 4.43 mcg/L (range: 1.3 to 16.5). The PCT level was<0.1 mcg/L in 14 patients, and 0.14 mcg/L in one patient. The percentage of volunteers with an undetectable PCT (defined as a value of <0.1 mcg/L) was 93%, and 100% of volunteers had PCT levels below the cut-offs typically associated with infection (0.15-2 mcg/L for localized mild-to-moderate bacterial infection and >2 mcg/L for severe bacterial infection). Table 1 displays the individual laboratory results. None of the participants developed an infection during the 2-week monitoring period.

S. no.	PCT (mcg/L)	CRP (mg/L)	ESR (mm/hour)	WBC (× 10^9/L)	Age (years)	Race	LVAD time (months)	Sex
1	<0.10	7.63	32	5.2	41	AA	5	M
2	<0.10	2.16	30	4.5	63	AA	39	M
3	<0.10	2.7	25	5.3	56	AA	2	M
4	<0.10	3.02	11	5.5	60	AA	8	M
5	<0.10	1.93	28	4.4	63	AA	2	M
6	<0.10	4.78	48	5.3	72	AA	37	M
7	0.14	1.39	15	5.4	43	AA	36	M
8	<0.10	1.75	11	6.4	72	AA	7	M
9	<0.10	3.49	8	5.9	72	AA	8	M
10	<0.10	3.51	71	4.9	50	AA	2	M
11	<0.10	4.8	45	5	45	AA	9	F
12	<0.10	2.38	25	2	55	AA	50	M
13	<0.10	9	40	3.5	66	AA	7	F
14	<0.10	16.5	39	8.7	48	WHITE	10	M
15	<0.10	1.53	15	9	63	AA	16	F

PCT=Procalcitonin; CRP= C-reactive protein; ESR= Erythrocyte sedimentation rate; WBC= White blood cell; LVAD= Left ventricular assist device; AA= African American.

Table 1: Procalcitonin and other inflammatory marker measurements in LVAD recipients.

Discussion

Our study confirms previous findings that some inflammatory levels may be elevated in non-infected LVAD recipients, but presents novel data regarding PCT levels. Elevated inflammatory levels in LVAD recipients presumably results from blood contacting the large, artificial surface with the resultant induction of an inflammatory cascade. One study demonstrated that blood exposure to an artificial surface induced chemokines, such as interleukin-8 and granulocyte-macrophage colony-stimulating factor, but not traditional pro-inflammatory cytokines, such as tumor necrosis factor alpha and IL-6 [6]. In another study comparing continuous-flow-LVAD with pulsatile-flow LVAD recipients, inflammation was elevated in both devices, with similar elevation in TNF-alpha levels, while the increase in IL-6 levels was higher in continuous flow patients [7]. In a more recent study comparing inflammatory markers in continuous flow-LVAD recipients to healthy controls, CRP, IP-10, MCP-1 and IL-8 levels were significantly higher in LVAD recipients [2].

In summary, our results confirm prior findings that non-specific markers of inflammation can be elevated in patients with an LVAD, and thus are poor biomarkers of infection. The finding of normal PCT levels in LVAD patients is important, as it suggests that this biomarker may prove useful as a marker of sepsis in this patient population. We hope that the results of our study will aide other investigators in developing a biomarker-based approach to the diagnosis of LVAD infections.

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Declaration of Interest

No affiliation (financial or otherwise) with a commercial organization that may have a direct or indirect connection to the content of the manuscript for any of the authors.

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