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Clinical Research

Longitudinal Assessment of Inflammation in Recipients of Continuous-Flow Left Ventricular Assist Devices

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ABSTRACT

Background: The long-term effects of continuous-flow left ventricular assist device (CF-LVAD) support on trends of inflammatory markers over time are unknown. We examined the hypothesis that the levels of inflammatory markers in CF-LVAD recipients are higher than in healthy controls and that these levels increase over time with long-term CF-LVAD support.

Methods: We examined the levels of inflammatory markers longitudinally at baseline before CF-LVAD implantation and at 3, 6, and 9 months after implantation. We then compared the levels of inflammatory markers to those in a healthy control group.

Results: Compared with baseline values before CF-LVAD implantation, left ventricular end-diastolic diameter (LVEDd) and left ventricular end-systolic diameter (LVESd) decreased significantly at 3, 6, and 9 months after CF-LVAD implantation. Brain natriuretic peptide (BNP) levels

RÉSUMÉ

Introduction : Les effets à long terme d'un soutien par un dispositif d'assistance ventriculaire gauche à flux continu (CF-LVAD) sur les marqueurs inflammatoires en fonction du temps ne sont pas connus. Nous avons examiné l'hypothèse que les taux de marqueurs inflammatoires chez les bénéficiaires d'un CF-LVAD sont plus élevés que chez les témoins sains et que ces niveaux augmentent avec le temps lors d'un soutien à long terme d'un CF-LVAD.

Méthodes : Nous avons examiné les niveaux de marqueurs inflammatoires longitudinalement au niveau basal avant l'implantation d'un CF-LVAD et à 3, 6 et 9 mois après l'implantation. Nous avons ensuite comparé les niveaux de marqueurs inflammatoires à ceux d'un groupe témoin sain.

Résultats : Par rapport aux valeurs de base avant l'implantation d'un CF-LVAD, le diamètre ventriculaire gauche télédiastole (LVEDd) et le

Inflammatory mediators contribute to the development and progression of heart failure.[1,2] These include cytokines, which are cell-signalling protein molecules that regulate inflammatory responses, and chemokines, which direct migration of leukocytes to the inflammation sites. From a clinical perspective, increased levels of inflammatory mediators are associated with deterioration of New York Heart Association (NYHA) functional classification.[3-6]

In recent years, left ventricular assist devices (LVADs) have increasingly been surgically implanted to provide mechanical support as a treatment for refractory heart failure. Given the growing evidence of increased patient survival with long-term support, LVADs have become an established therapy for patients with end-stage heart failure as a bridge to transplantation.[7,8] For patients ineligible for transplantation, LVAD support is a destination therapy.[9] In a very small number of patients, the LVADs have also been used as a bridge to recovery, allowing device removal without cardiac transplantation.[10] The newer generation of continuous-flow left ventricular assist devices (CF-LVADs) have been shown to confer some advantages over older pulsatile-flow LVADs (PF-LVADs), including durability, smaller size, fewer infections,[11] and a lower incidence of thromboembolic events.[12] However, the effects of low pulsatility on inflammatory mediators are not completely understood in CF-LVAD recipients.

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dropped significantly after CF-LVAD implantation but did not normalize. Improvements in ejection fraction at 3, 6, and 9 months after CF-LVAD implantation did not reach significance. Monocyte chemoattractant protein-1, interferon γ-induced protein, and C-reactive protein levels were higher in the CF-LVAD recipients at each of the time points (baseline before CF-LVAD implantation and 3, 6, and 9 months after implantation) compared with levels in healthy controls. In CF-LVAD recipients, serum interleukin-8, tumour necrosis factor-α, and macrophage inflammatory protein-β increased significantly at 9 months, and macrophage-derived chemokine increased at 6 months after CF-LVAD implantation compared with baseline.

Conclusions: Despite improvements in LV dimensions and BNP levels, markers of inflammation remained higher in CF-LVAD recipients. High levels of inflammation in CF-LVAD recipients may result from heart failure preconditioning or the long-term device support, or both. Because inflammation may be detrimental to CF-LVAD recipients, future studies should determine whether inflammatory pathways are reversible.

diamètre ventriculaire gauche en télésystole (LVESd) ont diminué de manière significative à 3, 6, et 9 mois après l'implantation d'un CF-LVAD. Les niveaux du peptide cérébral natriurétique sont sensiblement diminués après l'implantation du CF-LVAD mais ne retournent pas à la normale. Les améliorations de la fraction d'éjection à 3, 6 et 9 mois après implantation d'un CF-LVAD n'étaient pas significatives. Une protéine induite par l'interféron-γ : la Monocyte chemoattractant protein-1 (MCP-1), et les taux de protéine C-réactive étaient plus élevés chez les bénéficiaires d'un CF-LVAD à chacun des points temporels (ligne de base avant implantation de CF-LVAD et 3, 6 et 9 mois après l'implantation) par rapport aux niveaux des contrôles sains. Chez les bénéficiaires de CF-LVAD, l'interleukine-8 (ILK-8) sérique, le facteur de nécrose tumorale alpha (TNFα), et la protéine « macrophage inflammatory protein-β » sont augmentés de manière significative à 9 mois, et la chimiokine dérivée des macrophages est augmentée 6 mois après l'implantation du CF-LVAD par rapport à la ligne de base.

Conclusions : Malgré des améliorations dans les dimensions du ventricule gauche les niveaux du peptide cérébral natriurétique, les marqueurs de l'inflammation sont demeurés plus élevés chez les bénéficiaires de CF-LVAD que chez les témoins sains. Des niveaux élevés de l'inflammation chez les bénéficiaires de CF-LVAD peuvent résulter de préconditionnement dû à l'insuffisance cardiaque ou au soutien de l'appareil à long terme, ou les deux. Puisque l'inflammation peut être préjudiciable aux bénéficiaires de CF-LVAD, les futures études devraient déterminer si les voies inflammatoires sont réversibles.

Previous studies have shown that blood exposure to an artificial surface results in systemic inflammation, increasing interleukin-8 (IL-8), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1β (MIP-1β), interferon γ-induced protein-10 (IP-10), and granulocyte macrophage-colony stimulating factor (GM-CSF), but not the traditional proinflammatory cytokines tumour necrosis factor-α (TNF-α), interleukin-1β (IL-1β), or interleukin-6 (IL-6).[13-16] Moreover, compared with pulsatile devices, patients with CF-LVADs have been shown to have elevated levels of renin angiotensin aldosterone system (RAAS) neurohormones,[17] which are known to increase the levels of inflammatory markers in the setting of heart failure, including TNF-α, IL-1β, IL-6, IL-8, and MCP-1, as well as the marker of systemic inflammation C-reactive protein (CRP).[18-23]

Accordingly, we hypothesized that the levels of inflammatory markers in CF-LVAD recipients would be higher than in healthy controls and that these levels would increase over time with long-term CF-LVAD support. The aim of our study was to examine the levels of inflammatory mediators longitudinally starting at baseline before CF-LVAD implantation and at 3, 6, and 9 months after implantation and to compare these levels to those observed in healthy controls.

Methods

Patients and study design

Patients with heart failure who were candidates for CF-LVADs as a bridge to cardiac transplantation or as a destination therapy were recruited from the Heart Function Clinic at the Toronto General Hospital. Healthy controls were recruited using posters. All eligible study participants were between 40 and 65 years of age. Informed consent was obtained from each patient before participation in the study. Healthy control individuals were free of any known disease, including cardiovascular disease, kidney disease, and diabetes. Exclusion criteria for CF-LVAD recipients were (1) kidney failure requiring kidney replacement therapy or transplantation, (2) recent thromboembolism (within the past 3 months), (3) right ventricular failure, (4) liver failure, (5) stage 4 chronic kidney disease (glomerular filtration rate [GFR] < 30 mL/min/1.73 m^2), (6) right ventricular systolic pressure > 50 mm Hg (pulmonary artery systolic pressure that precludes transplantation) after CF-LVAD implantation, and (7) active systemic infection. We examined the levels of inflammatory mediators longitudinally at heart failure baseline before CF-LVAD implantation and at 3, 6, and 9 months after implantation and compared them to levels of inflammation in healthy controls. Throughout the longitudinal assessment, white blood cell counts were monitored and swabs for culturing were obtained from the driveline exit site to assess percutaneous driveline infection in the CF-LVAD recipients. CF-LVAD recipients were included in the analysis only if their white blood cell counts were within the normal range and no percutaneous driveline infection was present as indicated by swab culture results of driveline exit sites.

Biochemical assays

Blood samples were obtained during the visit to the Heart Function Clinic after a 12-hour fast and were collected in chilled tubes containing ethylenediaminetetra-acetic acid. The samples were then immediately centrifuged at 2056*g* for 15 minutes at 4°C and the plasma was stored at −80°C until analysis. Concentrations of the cytokines and anti-inflammatory