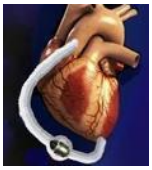

The VAD Journal: *The journal of mechanical assisted circulation and heart failure*

Peer-Reviewed Case series

Acute Appendicitis: A Potential Complication of Continuous-Flow Left Ventricular Assist Device Support

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Citation: Roark, J et al. (2016). "Acute Appendicitis: A Potential Complication of Continuous-Flow Left Ventricular Assist Device Support"

The VAD Journal, 2. doi: http://dx.doi.org/10.13023/VAD.2016.17

Editor-in-Chief: Maya Guglin, University of Kentucky

Received: June 6,2016

Accepted: August 16,2016

Published: August 16,2016

Funding: Not applicable

Competing interests: Not applicable

Abstract

Acute appendicitis, while common in younger patients, is an unusual cause for hospitalization among older adults. We report a case series of 3 individuals who had been previously implanted with a continuous-flow left ventricular assist device (CFLVAD) for end-stage heart failure, and who subsequently developed acute appendicitis. Both axial-flow technology and nonpulsatile systemic blood flow have been implicated as potential causes for bleeding and thrombosis in contemporary LVAD populations (13). This case series represents the first report of acute appendicitis as an adverse event following LVAD implantation and represents a patient demographic that would historically be at very low-risk for this illness. Our patients, their presentation, and the associated pathologic findings raise the possibility of a unique link between appendiceal inflammation and CFLVAD support that warrants attention.

Keywords: LVAD; appendicitis; Continuous flow left ventricular assist device; CF-LVAD; angiodysplasia; vWF; vWD; von Willebrand Deficiency

Introduction

Acute appendicitis is common and affects nearly one-quarter of a million Americans per year. It most often presents in patients between the ages of 10 and 19 years, with an overall rate of 235,000 cases/year in this demographic cohort

(4). We describe 3 unique cases of acute appendicitis that occurred in patients who had previously received a HeartMate II (Thoratec Corporation) LVAD (n=177) for management of end-stage systolic heart failure at our institution. The affected patients in our series ranged in age from 51 to 62 years – a demographic historically associated with a very low incidence of appendicitis (approximately 56 cases per 10,000 patients per year) (4). Although the cohort is small, we felt that the incidence is epidemiologically intriguing. This unusual cohort of patients raises the possibility that there may be a pathophysiological interaction between continuous systemic blood flow, axial-flow technology, and the subsequent development of appendiceal inflammation.

Case Presentation

The first patient was a 62 year old female with a past medical history of severe, chronic systolic heart failure, type II diabetes mellitus, chronic kidney disease, and hypertension who underwent LVAD placement with a HeartMate II (HM-II) axial-flow device. Prior to admission, the patient had a history of GI bleeding that was not characterized with EGD due to high risk of the procedure. Greater than 3 years after LVAD implantation, she presented to the Emergency Department (ED) with the acute onset of nausea, vomiting, and abdominal pain. The patient's exam was significant for pain localized to the right lower quadrant, with associated guarding and rebound tenderness. Her bowel sounds were diminished. Her laboratory analysis was notable for a leukocytosis (white blood cell count, WBC = 20.6 10*9/L). Her creatinine was stable at 2.41 mg/dL. A serum pro-B-type natriuretic peptide (proBNP) was elevated at 44,700 pg/mL. Lactate dehydrogenase (LDH) was stable at 768 U/L (normal 338610 U/L) and international normalized ratio (INR) was 2.0. Interrogation of her LVAD revealed settings of: flow 5.4, speed 9800 RPM (goal average speed in our population is 900010000), pulsatility index (PI) 6.4, and power 7.0. Unfortunately there was no echocardiographic or hemodynamic data available just prior to surgery. However, the patient's previous echo showed left ventricular hypertrophy with an ejection fraction of 45%, trivial mitral regurgitation, mild aortic regurgitation, mild pulmonary regurgitation and normal right ventricular performance. Both a urinalysis and blood cultures were obtained before the patient was started empirically on IV piperacillin-tazobactam (Zosyn) for broad-spectrum antimicrobial therapy. Given her persistent abdominal pain, a computed tomography (CT) scan was ordered. This revealed a ruptured appendix with a small area of peri-appendiceal gas and nearby fluid collection concerning for possible abscess. The patient's antimicrobial therapy was then broadened, and an emergent surgical consultation was requested. After evaluating the patient, the surgical team recommended percutaneous abscess drainage with plans to perform definitive appendectomy following patient stabilization. A drain was placed into the abscess approximately 2 days following admission to the hospital, and output was closely monitored. After transitioning to an oral antimicrobial regimen (including levofloxacin and metronidazole), the patient was discharged to home. Two weeks later, the drain was removed and the patient remained on antibiotics until the time of appendectomy, approximately 2 months later. At the time of removal, the appendix was described pathologically as having "submucosal fibrosis and fibrous scarring of the muscularis propria and peri-

appendiceal soft tissue, consistent with a prior episode of appendicitis." The patient tolerated the surgery well and made a full recovery.

The second patient was a 51 year old male with a past medical history of hypertension, hyperlipidemia, and end-stage systolic heart failure who received a HMII LVAD approximately 2 months prior to his presentation with acute appendicitis. The patient initially presented to the LVAD clinic with three days of worsening nausea, vomiting, and abdominal pain. His exam was significant for marked tenderness to palpation at McBurney's point and he was sent to the ED for further evaluation. There, he received a CT scan that showed an enlarged appendix with wall thickening, hyperenhancement, and periappendiceal inflammatory stranding. There was no free air surrounding the appendix or radiographic evidence of abscess formation. His laboratory values were significant for a normal WBC count of 5.8 10*9/L and INR of 2.5. Other significant laboratory values for this patient included an LDH of 1461 U/L and rose to 2122 U/L during hospitalization, proBNP of 1640 pg/mL, and total bilirubin of 1.9 mg/dL. LVAD settings showed flow 3.7, speed 8200 RPM, PI 5.8, and power not recorded. Echocardiogram at the time of admission showed mild contractile left ventricular dysfunction with an ejection fraction of 45%, elevated left ventricular pressures, dilated right atrium with a normal right ventricular contractile performance. The patient received 2 units of fresh frozen plasma to reverse the coagulopathy associated with his chronic Coumadin use, and he subsequently underwent urgent laparoscopic appendectomy. There were no complications with the surgery. Pathology showed a "7.1 cm long x 0.6 cm in diameter diffusely disrupted and torn vermiform appendix, along with a 2.5 x 1.2 x 0.4 cm aggregate of soft gray/tan tissue and red/brown blood clot. The serosa was gray and scabrous. The margin was inked green, and the wall was 0.1 cm thick. The lumen was patent with a red/brown mucosa." In summary, these findings were consistent with the patient's clinical diagnosis of acute appendicitis. He was treated with IV Meropenem and then transitioned to levofloxacin and metronidazole at discharge to complete a 14-day oral antibiotic course. The patient made a full recovery and was later transplanted.

The final patient was a 65 year old female with a past medical history of end-stage systolic heart failure, hypertension, and chronic kidney disease who was transplant-ineligible and therefore had a HM-II LVAD placed as destination therapy. The patient did have a history of bleeding and was started on thalidomide out of concern for angiodysplasia. Following 3.5 years of uncomplicated LVAD support, the patient began to notice low grade fevers. These symptoms persisted for 3-4 days and were associated with chills, fatigue, and generalized weakness. The patient also endorsed one week of right lower quadrant and epigastric abdominal pain that was sharp and non-radiating. Upon further questioning, she noted nausea and vomiting, decreased appetite, and diminished oral intake. With ongoing symptoms, the patient then presented to her primary doctor who prescribed oral Cephalexin to treat a presumed urinary tract infection. When this did little to alleviate her pain, she then presented to the ED for additional evaluation. Her laboratory studies there were significant for a neutrophil-predominant WBC count of 20.1 10*9/L, serum creatinine of 1.21 mg/dL, normal liver function tests, a proBNP 4680 pg/mL (increased from previous value of 388

two weeks earlier), INR 1.5, LDH was stable at 739 U/L (normal 338610 U/L) but rose during admission to 2411 U/L, and a venous lactate of 1.3 mmol/L. LVAD settings for her were flow 4.0, speed 9400 RPM, PI 3.9, power 5.6. Echocardiogram two weeks before presentation showed left ventricular hypertrophy with severe contractile dysfunction and ejection fraction of 25%, aortic sclerosis, degenerative mitral valve disease, and mild right ventricular dysfunction. No echo was done at the time of presentation.

She was started on IV Vancomycin, which was then changed to IV levofloxacin and metronidazole following hospital admission. A CT scan revealed acute appendicitis without evidence of perforation. The patient underwent an open appendectomy due to concerns that pneumoperitoneum, as part of a laparoscopic surgery, might lead to hemodynamic instability.

The patient's postoperative course was complicated by an adynamic ileus that resolved after six days of bowel rest. Surgical pathology of tissue fragments showed "a 5.5 x 0.6 cm tubular fragment of dark red/tan tissue with a dark red/purple external surface and no evidence of exudate or disruption. The presumed appendiceal tip was identified at one end. Sectioning revealed a patent lumen with markedly hemorrhagic wall". She remained on oral antibiotics for one month following discharge from the hospital. She made a full recovery and is still on LVAD support at this time.

Discussion

Acute appendicitis, while common among children, teenagers, and young adults, is considerably less common among older patients. While more recent epidemiologic data has suggested that rates among those 50-69 years old have begun to slowly increase over time (5) owing to longer patient lifespans and better diagnostic tools - the development of appendicitis in 3 out of 177 of our HeartMate II LVAD patients would be considered epidemiologically unusual (Figure 1). Unfortunately, there was no data while reviewing the epidemiology of appendicitis incidence that details how many of these patients suffered from heart failure, hypertension, diabetes, stroke or other medical chronic medical conditions therefore statistical comparisons between these groups could not be performed. This unexpected finding raises the possibility of a pathophysiologic link between CF-LVAD support and the development of appendiceal injury.

It has been previously demonstrated that patients with CF-LVADs have increased circulating markers of inflammation. This is thought to be due to blood-device interactions and the influence of continuous (as opposed to pulsatile) blood flow (6). It is also known that acquired von Willebrand Deficiency (vWD) (7) and angiodysplasias (1) - each well-described complications of axial-flow LVADs – can lead to intestinal ischemia. The pathogenesis of angiodysplasias in the gastrointestinal tracts are not fully understood. The imbalance of proangiogenic and antiangiogenic factors plays a large role. The leading cause is thought to be venous congestion caused by low output states (as in patient with LVADs) in the submucosa that is translated to capillary congestion and formation of arteriovenous collaterals through increased VEGF secretion (8). In addition, these

angiodysplastic changes are most commonly found in the peri-appendiceal portion of the gastrointestinal tract (9). LVADs are known to lead to arteriovenous

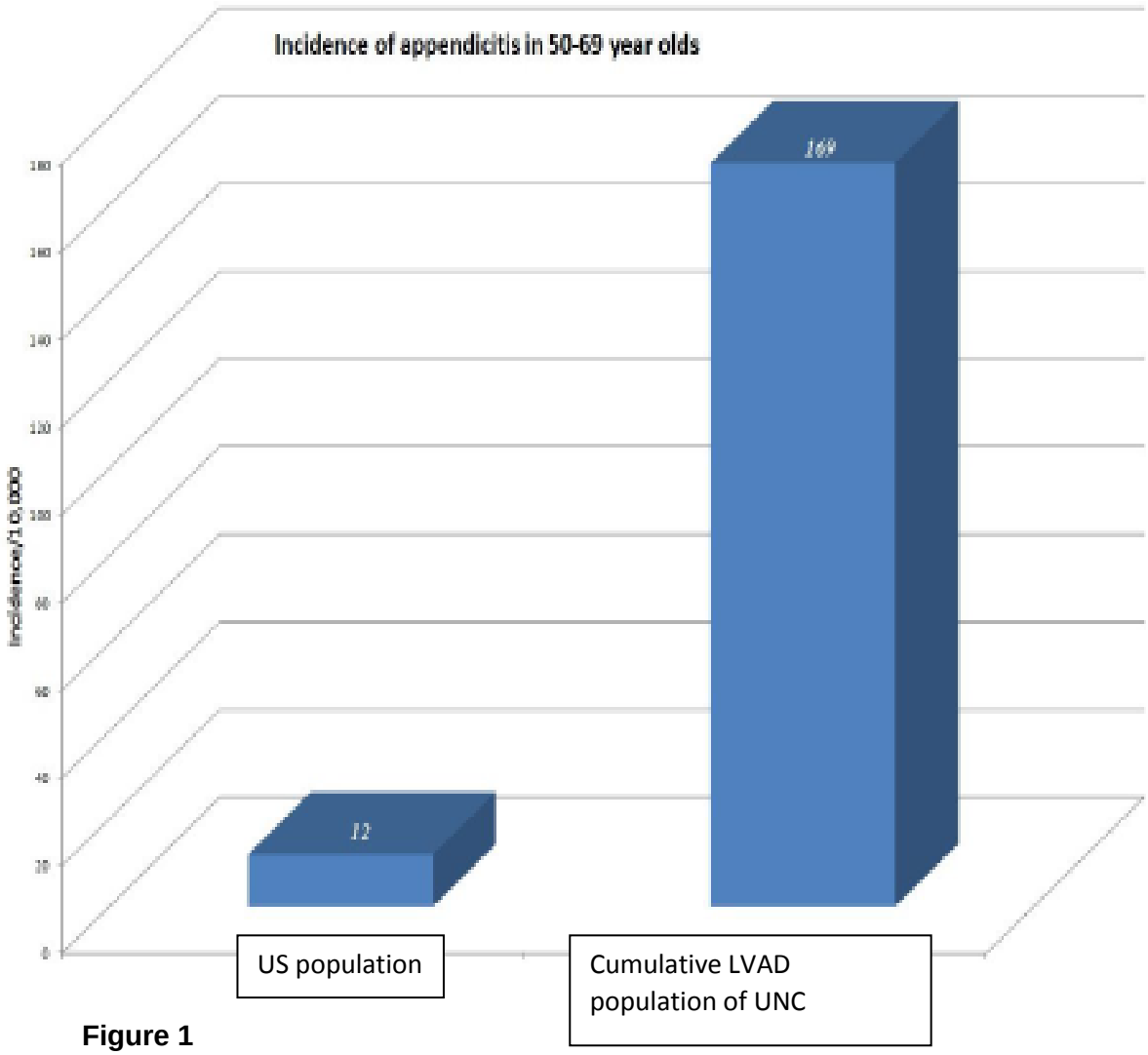

Figure 1

Incidence of appendicitis in 50-69 year olds

malformations (10) and are known to occur more frequently in patients without pulsatile flow. One could then postulate that the combined effects of enhanced systemic inflammation and ischemia arising from the low, non-pulsatile flow state combined with venous congestion, acquired vWD, and formation of arteriovenous malformations could lead to a lower threshold for the sudden development of acute appendicitis (Figure 2) in the setting of intraluminal obstruction. This has been demonstrated in case reports of children that have presented with acute appendicitis and were later revealed to have arteriovenous malformations (11, 12). Further supporting this notion is the fact that each of the patients described above

had a documented history of gastrointestinal bleeding after CF-LVAD implantation. Due to the high risk nature of further procedures in patients with LVADs, esophagogastroduodenoscopy was not performed for any of the patients and they were managed conservatively with discontinuation of anticoagulation. In each of the cases, the bleeding resolved with this intervention. In summary, although we have proposed a model for this, fully developing the pathophysiological model would likely require more data from patients in this population.

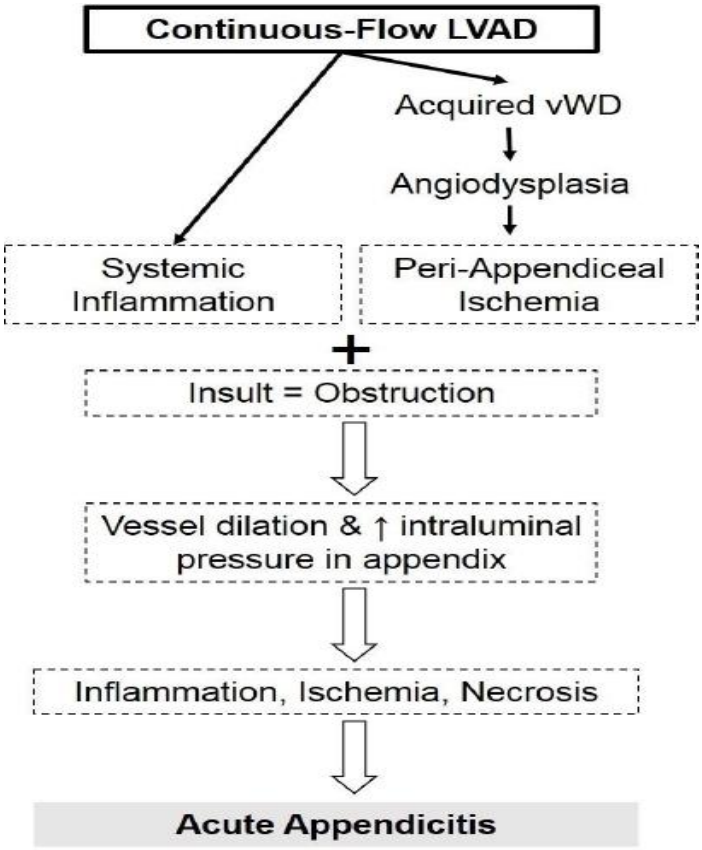

Figure 2

Proposed pathogenesis of acute appendicitis in LVAD

We believe that this is the first reported case series of acute appendicitis following implantation of a CF-LVAD, and adds to a growing list of potential adverse events among patients supported with these durable devices. While certainly not as common as bleeding, thrombosis, driveline infection, or arrhythmias, appendicitis should not be considered a benign complication. Management almost always requires operative intervention, and this increases the risk for driveline injury, sepsis, bleeding, and death among these high-risk individuals. In addition, the need to discontinue and even reverse systemic anticoagulation for preoperative preparation also puts the device and patient at risk for thrombotic complications, including LVAD malfunction, hemolysis, and stroke. As the volume of LVAD implants continues to escalate, a better understanding of the potential mechanism

of appendiceal injury and an increased awareness of the potential link between LVADs and the subsequent development of acute appendicitis is warranted.

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