Low incidence of gastrointestinal bleeding and pump thrombosis in patients receiving the INCOR LVAD system in the long-term follow-up

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ABSTRACT

Background: Left ventricular assist device (LVAD) implantation improves survival and quality of life in patients with advanced heart failure (HF). Despite these advantages, LVADs are not free from risks. Among all adverse events (AE), pump thrombosis and bleeding, especially of the gastrointestinal (GI) tract, have been reported to occur with increasing frequency in some CF-LVADs. The INCOR LVAD system is a third-generation, continuous flow, axial pump with active magnetic levitation, avoiding the potential downsides of mechanical bearings.

Methods: The aim of this retrospective study was to review the Italian clinical experience with the INCOR LVAD and to determine the prevalence of GI bleeding and pump thrombosis. All patients implanted between January 2006 and May 2012 were considered eligible.

Results: The total population consisted of 42 patients. LVAD indication was BTT in 36 (86%) and DT in 6 (14%) patients; 31 patients (74%) were INTERMACS class 1 or 2. Mean support time was 525 ± 570 days. The 1-year and 2-year survival rates were 74% and 60%, respectively. The most frequent AE was driveline infection (0.33 events PPy) followed by stroke with consequence (0.17 events PPy), sepsis (0.07 events PPy), and right HF (0.05 events PPy). No episodes of pump thrombosis or GI bleeding were observed.

Conclusions: In this cohort of high-risk, advanced HF patients, the INCOR LVAD provided effective support with improved survival. Moreover, the absence of GI bleeding and pump thrombosis demonstrates a favorable characteristic of this device. Further prospective studies are needed to confirm these data.

Keywords: Left ventricular assist device, Advanced heart failure, Gastrointestinal bleeding, Pump thrombosis

Introduction

Continuous-flow, left ventricular assist device (LVAD) implantation is an established therapy for patients with advanced heart failure (HF) (1). For inotrope-dependent patients this treatment has been included in the current international HF guidelines as a class I indication for bridge to transplantation (BTT) or destination therapy (DT) (2). LVADs, mechanically assisting the left ventricle, increase the cardiac output, thus improving patients’ survival and quality of life (3). Data analysis from the North-American LVAD registry INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) has provided important information about survival and adverse events (AE) for different types and generations of LVADs (4). During recent years the incidence of pump thrombosis and major bleeding, especially gastrointestinal (GI) bleeding, has significantly increased (5-6). From a current meta-analysis based on 17 studies, the pooled incidence rate for GI bleeding in the 1687 patients with continuous-flow LVAD therapy was 23% (7). Recently, along the same lines, pump thrombosis rates of 12.3% were reported during 24 months of support with HeartMate II (6), and 8.1% with HVAD (8). The etiology of these frequent complications is not completely understood and appears to be multifactorial.

The INCOR LVAD system (Berlin Heart GmbH, Berlin, Germany) introduced in 2002 is the first CE-approved, third-generation, axial flow pump with a fully magnetically levitated suspension. It operates without any mechanical
contact and ensures wear-free, long-term support. Major improvements of the device and the software were introduced starting in 2005: the short inflow cannula of the LVAD was replaced by a longer one, and new software features were implemented, such as suction protection and periodic flow change (PFC), taking advantage of the magnetic levitation that permits rapid impeller speed modulations (9). The PFC software feature provides periodic pump flow modulation and, as a consequence, promotes aortic valve opening, improves washout of the left ventricle, and prevents aggregation of deposits in the pump. The aim of this study was to review the Italian experience with the INCOR system and to define the prevalence of GI bleeding and pump thrombosis.

Method

Study design and patient population

This study is an Italian, multicenter, retrospective evaluation of patients who underwent implantation of the INCOR LVAD from January 2006 to May 2012. Patients with advanced heart failure (HF) classified in INTERMACS levels as less than 1 to 4, and treated as BTT or DT in Italian centers with at least 5 implants were considered eligible. Exclusion criteria were age below 18 years and patients supported by biventricular VAD. The study was conducted according to the Declaration of Helsinki and in adherence with ICH-GCP guidelines. The demographic and clinically relevant preoperative, postoperative and long-term follow-up data were collected using local internal databases, patient charts, and hospital admittance details from the participating centers. Hemodynamic measurements before LVAD surgery were performed as part of routine perioperative care. All adverse events, including those meeting the INTERMACS definition (www.uab.edu/medicine INTERMACS), were evaluated. GI bleeding was defined as the presence of melena, hematochezia, or hematemesis along with a drop in hemoglobin requiring blood transfusion. Suspected pump thrombosis required at least 2 of the following criteria to be met: the presence of hemolysis, HF not explained by structural heart disease, and abnormal pump parameters. Confirmed pump thrombosis was defined as a pump malfunction in which a thrombus is confirmed within the blood-contacting surfaces of the device inflow cannula, outflow conduit, or graft.

Information about aortic insufficiency (AI) was collected by a specific echocardiographic questionnaire sent to every center. The severity of AI was assessed by color Doppler flow mapping of the LV outflow tract and classified as mild, moderate, or severe. Patients were followed up according to each individual institutional protocol. Anticoagulation regimes, as suggested by Berlin Heart GmbH, were titrated, maintaining an international normalized ratio (INR) range of 2.5 to 3 combining platelet inhibitors (acetylsalicylic acid and/or clopidogrel and/or dipyridamol). The appropriate dosage of antplatelet therapy was adjusted using thromboelastography and aggregometry. Ethical committee approval was waived because of the retrospective nature of the study using routine data (Law no. 11960, issued on July 13, 2004).

Statistical analysis

Continuous variables demonstrating a normal distribution are expressed as mean ± standard deviation (SD). Continuous variables demonstrating a non-normal distribution additionally are expressed as mean ± SD and median (with minimum and maximum). Categorical variables are reported as absolute and percentage frequency values, or, in the case of adverse events, are standardized and reported as events per patient year (EPPY). The Kaplan-Meier actuarial survival estimate was generated to analyze post-LVAD survival of the entire cohort at 1 year and 2 years. We included the following independent variables in univariate and multivariate logistic regression analyses of mortality: age, gender, height, weight, body surface area, etiology of heart failure, INTERMACS category (ungraded/grouped), strategy (BTT/DT), atrial fibrillation, aortic regurgitation, anticoagulation use, extracorporeal membrane oxygenation support (ECMO) use, dialysis use, mechanical ventilation use, cardiac output (CO), EF (ejection fraction), cardiac index (CI), pulmonary vascular resistance (PVR), systolic pulmonary arterial pressure (SPAP), mean pulmonary arterial pressure (MAP), mean arterial pressure (MAP), central venous pressure (CVP), systemic vascular resistance (SVR), pulmonary capillary wedge pressure (PCWP) and CVP/PCWP ratio. To provide a cutoff point for the CVP/PCWP ratio, this continuous variable was converted into a categorical variable, and multiple serial χ² testing was performed with a stepwise threshold progression to determine maximal divergence between survivors and nonsurvivors. All data were analyzed using Statistical Package for Social Sciences, version 17.0 (SPSS Inc., Chicago, IL, USA).

Results

Between January 2006 and May 2012, 46 INCOR LVAD systems were implanted in 6 Italian centers, of which 4 centers (Papa Giovanni XXIII Hospital (former Ospedali Riuniti Bergamo), Ospedale Molinette Turin, Niguarda Hospital of Milan, Santa Maria Misericordia Hospital of Udine) implanted at least 5 INCOR LVADs and were selected as participants in the study. The total population consisted of 42 patients. LVAD indication was reported to be BTT in 36 (86%) patients and DT in 6 (14%) patients. Baseline demographic and clinical data are summarized in Table I. Thirty-nine patients were male (93%), and the mean age was 56 ± 8.3 (35 to 70) years. The cause of HF was idiopathic in 21 patients (50%), ischemic in 19 patients (45%), and toxic cardiomyopathy in 2 patients (5%); 31 patients (74%) were in INTERMACS class 1 or 2, among whom 10 (24%) patients required ECMO. Preoperative hemodynamic and left ventricular function was consistent with a group of patients with advanced HF (Tab. II).

Support durations

After LVAD placement, 37 patients (88%) were discharged home; the mean time to discharge was 56 ± 34 days, median 53 (14-148) days with a maximum time on device reaching 7.4 years. The mean support duration was 525 ± 570 days, median 372 (5 to 2704) days, the cumulative time on device was 60.3 years.
TABLE I - Patients characteristics PRE-LVAD implantation of 42 study patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (range)</td>
<td>56 (35-70)</td>
</tr>
<tr>
<td>Male, no. (%)</td>
<td>39 (93)</td>
</tr>
<tr>
<td>Body surface area m² - no. (range)</td>
<td>2 (1.5-2.6)</td>
</tr>
</tbody>
</table>

Etiology
- Idiopathic CMP - no. (%)     | 21 (50)  
- Ischemic CMP - no. (%)       | 19 (45)  
- Toxic CMP - no. (%)          | 2 (5)    

Indication
- BTT - no. (%)                | 36 (86%)  
- DT - no. (%)                 | 6 (14%)   

INTERMACS profile
- 1 - no. (%)                  | 17 (41)   
- 2 - no. (%)                  | 14 (33)   
- 3 - no. (%)                  | 8 (19)    
- 4 - no. (%)                  | 3 (7)     

Concomitant intervention
- Mechanical ventilator - no. (%) | 22 (52)  
- Dialysis - no. (%)            | 7 (17)    
- ECMO n (%)                    | 10 (24)   
- Re-Thoracotomy n (%)          | 1 (2)     

CMP = cardiomyopathy; BTT = bridge to transplantation; DT = destination therapy; ECMO = extracorporeal membrane oxygenation.

TABLE II - Preoperative hemodynamic data of 42 study patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP, mmHg</td>
<td>70 ± 8</td>
</tr>
<tr>
<td>CVP, mmHg</td>
<td>12 ± 6</td>
</tr>
<tr>
<td>SPAP, mmHg</td>
<td>42 ± 12</td>
</tr>
<tr>
<td>MPAP, mmHg</td>
<td>29 ± 9</td>
</tr>
<tr>
<td>PCWP, mmHg</td>
<td>21 ± 6</td>
</tr>
<tr>
<td>PVR, WU</td>
<td>163 ± 185</td>
</tr>
<tr>
<td>CVP/PCWP, mmHg</td>
<td>0.56 ± 0.24</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>18 ± 5</td>
</tr>
<tr>
<td>CO, l/min</td>
<td>3.6 ± 0.8</td>
</tr>
<tr>
<td>CI, l/min/m²</td>
<td>1.9 ± 0.5</td>
</tr>
</tbody>
</table>

MAP = mean arterial pressure; CVP = central venous pressure; SPAP = systolic pulmonary arterial pressure; MPAP = mean pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; LVEF = left ventricular ejection fraction; CO = cardiac output; CI = cardiac index; PVR = pulmonary vascular resistance.

The 42 patients were transplanted, 1 (2%) patient regained myocardial function and had the device removed, 19 (45%) of the 42 patients died while being on support. At last follow-up (July 2014), 5 (12%) patients were still on device support. With the use of competing outcomes methodology, these results are displayed in Figures 1A and B. Patients were transplanted after a mean of 375 ± 246 days, and a median of 367 (16 to 832) days of support. For the patients who died during the observation period, death occurred after a mean of 383 ± 421 days, and a median of 297 (5-1698) days on support.

**Cause of death and adverse events**

In the 19 patients who died, the most frequent causes were hemorrhagic stroke in 6 (32%) patients, followed by sepsis in 4 (21%) patients. Three patients (16%) died from bleedings that were not gastrointestinal (1 patient had a peritoneal bleeding after injection of subcutaneous low molecular-weight heparin, 1 had massive bleeding due to a pseudoaneurysm caused by a tear in the aortic wall provoked by a stitch, and 1 patient after cholecystectomy). Three (16%) patients died from right ventricular failure after 5 to 712 days, 2 (10%) patients from unexplained sudden death not related to device malfunction, and 1 patient (5%) from ischemic stroke. The most frequently observed AE was driveline infection (0.33 events PPy) followed by stroke with sequelae (0.17 events PPy), sepsis (0.07 events PPy), and right HF (0.05 events PPy). No episodes of pump thrombosis or GI bleeding were observed. Since 2011, the length of the driveline velour was adapted to anatomical conditions ensuring that only the silicone section is exposed at the
percutaneous exit site. Of 4 patients with the redesigned driveline only 1 patient experienced a driveline infection. Before LVAD implantation AI was present to a mild degree in only 7 (17%) patients; during the follow-up, AI worsened to moderate levels in only 2 patients (Fig 2).

**Predictor of mortality**

Table III shows the predictors of postoperative mortality in univariate analysis. Dialysis was a statistically significant independent predictor of mortality after LVAD implantation (Odds Ratio [OR], 10.15; 95% confidence interval [CI], 1.10-93.98, P<.04). Multivariate analysis of predictors for postoperative mortality identified BTT strategy (OR, 0.08; 95% CI, 0.008-0.852, P<.04) and CVP/PCWP-ratio (OR, 25.66; 95% CI, 1.02-640.52, P<.05) (cut-off .57) as significant predictors of mortality (Tab. IV).

**Discussion**

The results of the present study show that after the main modification of the outflow cannula and software implementation, the INCOR LVAD system can effectively support patients even with predominantly low INTERMACS levels, with no episodes of GI bleeding and pump thrombosis. Gastrointestinal bleeding and pump thrombosis are the most common severe AEs in the treatment with LVADs and seem to be associated with an unfavorable long-term clinical outcome (5, 10). Recent experience has also shown a significant increase in the incidence of pump thrombosis in the latest generation of LVAD devices. Patients supported by HeartMate II suffered from a rate of up to 12.3% pump thrombosis during 24 months of support, with a high mortality among patients not treated by device replacement or heart transplantation (6). Several explanations have been proposed, including implantation technique, anatomical constraints, infections, pump setting, and level of anticoagulation. However, the most credible reason appears to be the technical characteristics of the pump (6, 11).

In the HeartMate II LVAD, the rotor is suspended with a mechanical bearing on spherical surfaces rotating in a socket. Deposits of fibrin and denatured protein have been observed in these pumps after thrombosis in proximity to the inflow bearing, which depends on fluid for lubrication and flow to dissipate heat. The INCOR LVAD uses an active electromagnetic levitation system that allows for complete absence of friction forces (Fig 3). This could be one possible explanation for the lack of pump thrombosis observed in our series of patients. Further, the blood-conducting parts of the INCOR blood pump are coated with a CBAS heparin surface. The CBAS coating has shown to reduce the extent of thrombotic pump deposits in pulsatile, paracorporeal VAD systems (12).

To confirm and strengthen those findings we reviewed the data of previous experience with the INCOR system and found almost 300 patients studied who had similar results (9, 13, 14). Starting in 2005 the inflow cannula was replaced by a longer one aimed at reducing the rate of thromboembolic complications. After this main change, to analyze the effect of the new cannula, a total of 216 consecutive patients were retrospectively analyzed in a multicenter study comparing 138 patients with short inflow cannula and 78 patients with a long inflow cannula. The results of the study showed again no episodes of GI bleeding or pump thrombosis (9).
In our study we found similar results but within a longer follow-up period; moreover, the new software functions, including PFC, were used in almost all patients. Gastrointestinal bleeding across studies with LVAD devices is the most commonly reported location of bleeding in the long-term follow-up, and is considered an important source of morbidity, resulting in repeated hospitalizations.

Angiodysplasia, impaired platelet aggregation, and a newly identified acquired von Willebrand syndrome have all been proposed as possible mechanisms responsible for GI bleeding events (15). All these postulated mechanisms seem to be related to the increased shear stress and loss of pulsatility in patients assisted by a continuous flow LVAD (16). In our study and in several previous publications of retrospective experiences with the INCOR system, only 1 episode of GI bleeding in almost 300 patients has been reported and only before the implementation of the new pump design, described above. This absence of gastrointestinal bleeding observed with this LVAD could be explained by the unique mechanical and software characteristics of the INCOR system. The active magnetic levitation allows the shear stress and heat in the pump to be significantly decreased. Both factors are considered to cause degradation of VWF multimers observed with LVADs of second generation and in centrifugal flow LVADs (16-18). Unfortunately von Willbrand factor degradation in our cohort of patients was not assessed, therefore only a prospective study could confirm this relationship.

The specific software algorithms aimed to increase pulsatility, including periodic flow modulation and pulsatility control (automatic reduction of the speed in the presence of low pulsatility), were implemented in the INCOR LVAD system in order to open the aortic valve intermittently, decreasing the speed of the pump. This periodic speed modulation could theoretically increase pulsatility and shear stress and may reduce the formation of intestinal acquired angiodysplasia. Aortic insufficiency after LVAD implantation reduces the efficacy of the pump and decreases cardiac output. AI development following LVAD implantation has been associated with aggravation of heart failure symptoms. Different mechanisms have been postulated to explain the progression of AI during LVAD support. Loss of pulsatility seems to be one of the most important reasons. Interestingly, in our series of patients supported by the INCOR system we could not see a significant progression of aortic insufficiency during follow-up and the aortic valve remained open in the majority of the patients. This finding could be at least partially attributed to the unique periodic flow change algorithm implemented in the INCOR system. The PFC software algorithm has shown to be safe and effective in the prevention of the fusion of the aortic valve during the long-term follow-up. However, controlled prospective studies are needed to confirm these findings.

In summary this multicenter, retrospective study confirms that the INCOR system is effective in supporting patients with advanced heart failure. The mechanical design and innovative software characteristics of this LVAD seem to reduce the rate of GI bleeding and pump thrombosis efficiently, complications that have been increasing over the last years with other LVADs. Moreover, no progression of AI in this cohort was seen with the INCOR LVAD. Further studies are necessary to prove these findings.

Disclosures

Financial support: None.
Conflict of interest: None of the authors has any financial interest related to this study.

References

2. McMurray JJ, Adamopoulos S, Anker SD, et al; Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology; ESC Committee for Practice Guidelines. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2012;14(8):803-869.


