Management of intracranial hemorrhage in patients with left ventricular assist devices

Clinical article

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Object. The authors conducted a study to review outcomes and management in patients in whom intracranial hemorrhage (ICH) develops during left ventricular assist device (LVAD) therapy.

Methods. This retrospective cohort study included all adult patients (18 years of age or older) at a single institution who underwent placement of an LVAD between January 1, 2003, and March 1, 2012. The authors conducted a detailed medical chart review, and data were abstracted to assess outcomes in patients in whom ICH developed compared to those in patients in whom ICH did not develop; to compare management of antiplatelet agents and anticoagulation with outcomes; to describe surgical management employed and outcomes achieved; to compare subtypes of ICH (intraparenchymal, subdural, and subarachnoid hemorrhage) and their outcomes; and to determine any predictors of outcome.

Results. During the study period, 330 LVADs were placed and 36 patients developed an ICH (traumatic subarachnoid hemorrhage in 10, traumatic subdural hematoma in 8, spontaneous intraventricular hemorrhage in 1, and spontaneous intraparenchymal hemorrhage in 17). All patients were treated with aspirin and warfarin at the time of presentation. With suspension of these agents, no thromboembolic events or pump failures were seen and no delayed rehemorrhages occurred after resuming these medications. Intraparenchymal hemorrhages had the worst outcomes, with a 30-day mortality rate in 59% compared with a 30-day mortality rate of 0% in patients with traumatic subarachnoid hemorrhages and 13% in those with traumatic subdural hematomas. Five patients with intraparenchymal hemorrhages were managed with surgical intervention, 4 of whom died within 60 days. The only factor found to be predictive of outcome was initial Glasgow Coma Scale score. No patients with a Glasgow Coma Scale score less than 11 survived beyond 30 days. Overall, the development of an ICH significantly reduced survival compared with the natural history of patients on LVAD therapy.

Conclusions. The authors’ data suggest that withholding aspirin for 1 week and warfarin for 10 days is sufficient to reduce the risk of hemorrhage expansion or rehemorrhage while minimizing the risk of thromboembolic events and pump failure. Patients with intraparenchymal hemorrhage have poor outcomes, whereas patients with traumatic subarachnoid hemorrhage or subdural hematoma have better outcomes.

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Key Words • intracranial hemorrhage • ischemic stroke • left ventricular assist device • vascular disorders

Heart failure affects approximately 6 million people in the United States8 and is associated with significant morbidity and mortality. In fact, the 1-year mortality rate for patients diagnosed with heart failure is approximately 25%.1,9 The prognosis is even graver in cases of advanced heart failure: patients with New York Heart Association Class IV heart failure have a 1-year mortality rate of approximately 75%.1,9 Traditionally, therapy for heart failure has included medical management and, in advanced stages, transplantation. However, the use of LVADs is becoming increasingly common, and what began as a treatment modality designed as a bridge to transplantation is now being increasingly used as a bridge to decision and as destination therapy.

Neurological complications of LVAD therapy include both ischemic stroke and ICH. Patients are often treated with both anticoagulation and antiplatelet agents to reduce the risk of ischemic stroke. However, these agents increase the risk of ICH, particularly in the setting of supratherapeutic anticoagulation levels.3,10 As use of LVADs increases, management of these LVAD-related complications is also becoming more common. Few data are available to guide decision making for the manage-

Abbreviations used in this paper: GCS = Glasgow Coma Scale; GOS = Glasgow Outcome Scale; ICH = intracranial hemorrhage; INR = international normalized ratio; IQR = interquartile range; LVAD = left ventricular assist device.

This article contains some figures that are displayed in color online but in black-and-white in the print edition.
ment of patients in whom ICHs develop in the setting of LVAD therapy, particularly with regard to surgical management, management of antiplatelet and anticoagulation medications, and prognostic guidance for patients and their families. The aim of this study was to examine LVAD-related ICHs, particularly with respect to management and outcomes, to provide additional information that may prove helpful to the neurosurgeon when treating this challenging condition.

Methods

Study Design

This cohort study was approved by the University of Michigan Institutional Review Board, and data were obtained by retrospective review of medical records including radiographic images. Information technology personnel designed and implemented a search paradigm to query the University of Michigan information systems and electronic medical records to identify all adult patients (18 years of age or older) who underwent placement of an LVAD between January 1, 2003, and March 1, 2012. In all cases a preliminary chart review was conducted to confirm LVAD placement.

From this population of patients, a detailed chart review was performed, and the following data were abstracted for all patients: age at time of LVAD placement, sex, race, date of LVAD placement, LVAD type (continuous or pulsatile flow), outcome of the LVAD (reason for removal or death), date of LVAD removal or death, antiplatelet therapy, anticoagulation therapy, and occurrence of an ICH or clinically significant ischemic event. For all patients in whom an ICH occurred, the following data were abstracted: hemorrhage location (subarachnoid, intraventricular, subdural, or intraparenchymal), date of hemorrhage, hemorrhage size, midline shift on head CT scan, expansion of hemorrhage after initial head CT scanning, initial GCS score, management plan employed, GOS score (1 = dead, 2 = vegetative state, 3 = severely disabled, 4 = moderately disabled, and 5 = good recovery) at 6 months and 1 year posthemorrhage, date of death, and cause of death. Volume of hemorrhage was calculated by multiplying the length × width × height and dividing by 2. The length and width of the hemorrhage were measured on the axial CT slice where the hemorrhage was largest, and height was determined by counting the number of CT slices containing hemorrhage and multiplying by slice thickness. Patients undergoing reversal of antiplatelet agents were managed by administration of platelet transfusions, whereas patients undergoing reversal of warfarin therapy were managed by administration of fresh-frozen plasma. No patients in this study were lost to follow-up.

Subgroup analysis was then performed, comparing the outcomes for each subtype of hemorrhage including subdural, subarachnoid, and intraparenchymal.

Statistical Analysis

Statistical analysis was performed using commercially available software (SPSS version 18, IBM Corp.). Univariate analysis of continuous variables with a normal distribution was done using 2-sample t-tests, and continuous variables not meeting the normality assumption were assessed using the Mann-Whitney U-test. All categorical data were assessed by chi-square test or Fisher exact test, as appropriate. Logistic regression was used to test univariate and multivariate associations between our variables of interest and the dichotomous outcome of death. Kaplan-Meier analysis was used to create survival curves, and survival curves were compared using the log-rank (Mantel-Cox) test. For all statistical analyses, p < 0.05 was considered significant.

Results

Baseline Characteristics

During the study period, 330 patients underwent placement of an LVAD. Of these patients, 36 (11%) suffered an ICH during dwell time of the LVAD. One ICH occurred per 4018 days of LVAD dwell time. Among patients suffering an ICH, the average time from LVAD placement to ICH was 300 days. Table 1 shows baseline characteristics for the overall cohort, the subpopulation of patients suffering an ICH, and the subpopulation of patients free of ICH. There was no difference in age, sex, race, or LVAD type between those patients who had an ICH and those patients who did not. Among patients in whom an ICH developed, 15 (42%) died prior to removal of the LVAD or transplantation, 12 (33%) underwent cardiac transplantation after the ICH occurred, 1 (3%) was able to have the LVAD removed after recovery of cardiac function, and 8 (22%) continued to be maintained on LVAD therapy at the time of this analysis.

Descriptive Statistics of ICHs

Of the 36 ICHs occurring during the study period, 10 (28%) were subarachnoid hemorrhage, all of which were traumatic in origin; all traumas were falls from standing height. Eight (22%) were subdural hematoma, and all were traumatic in origin; in 6 cases, the patients suffered a fall from standing height and in 2 the patients were involved in minor motor vehicle accidents. One (3%) of the ICHs was an intraventricular hemorrhage in the absence of preceding trauma; no vascular abnormality was discovered to account for this hemorrhage. Finally, 17 (47%) of the ICHs were intraparenchymal hemorrhage, all of which were spontaneous hemorrhages without any preceding trauma.

One subdural hematoma occurred for every 18,081 LVAD days. The average age of patients in whom a subdural hematoma occurred was 52 years (IQR 23 years). The average maximal thickness of the subdural hematoma was 10 mm (range 6–20 mm). The average midline shift observed at the time of presentation was 4 mm (range 0–16 mm). The average GCS score at presentation was 13 (range 6–15), with an IQR of 5. All patients were on aspirin and warfarin therapy at time of presentation. The average INR at presentation was 1.6 (range 1.0–3.6), with an IQR of 1.0.
One intraparenchymal hemorrhage occurred for every 9040 LVAD days. The average age of patients in whom an intraparenchymal hemorrhage occurred was 54 years (IQR 15 years). The average volume of the intraparenchymal hemorrhage was 52 cm$^3$ (range 0–191 cm$^3$, IQR 115 cm$^3$). The average midline shift observed at presentation was 6 mm (excluding 2 hematomas within the cerebellum; range 0–14 mm, IQR 9 mm). The average GCS score at presentation was 9 (range 3–15, IQR 10). All patients were on aspirin and warfarin therapy at presentation. The average INR at presentation was 1.7 (range 1.0–5.1, IQR 0.9). Only 1 patient had a supratherapeutic INR (average INR at presentation was 1.7 (range 1.0–5.1, IQR 0.9)). Notably, no pump failures or clinically significant ischemic events were observed in any patients in whom aspirin or warfarin was withheld. No delayed rehemorrhages were observed after resuming aspirin and warfarin therapy.

**Management and Outcomes**

All patients who presented with ICH were being treated with aspirin and warfarin at time of presentation. Table 2 summarizes the management of aspirin and warfarin and the outcomes relative to platelet inhibition and anticoagulation. Notably, no pump failures or clinically significant ischemic events were observed in any patients in whom aspirin or warfarin was withheld. No delayed rehemorrhages were observed after resuming aspirin and warfarin therapy.

Table 3 summarizes outcomes in patients presenting with ICH. Patients presenting with an intraparenchymal hemorrhage had the worst outcomes, with a mortality rate of 59% within 30 days and a median GOS score of 1 at both 6 months and 1 year. Comparatively, no patients died after traumatic subarachnoid hemorrhage by 30 days and only 13% died by 30 days following a traumatic subdural hematoma. In general, patients with a traumatic subdural hematoma or traumatic subarachnoid hemorrhage had good outcomes, with median GOS scores at 1 year of 3.5 and 5, respectively.

Of the 17 patients who had an intraparenchymal hemorrhage, 5 underwent operative intervention: craniotomies for clot evacuation in 2, and hemicraniectomies for clot evacuation in 2, and hemicraniectomies and craniectomies for clot evacuation in 3. Four (80%) of these 5 patients died within 60 days. The median GOS score at 6 months for patients undergoing operative intervention was 1 (range 1–3); similarly, at 12 months the median score was 1 (range 1–3).

Within the subpopulation of patients who developed intraparenchymal hemorrhage, operative intervention did not alter the risk of death (p = 0.238). Similarly, there was no association between INR (p = 0.289), time between LVAD placement and hemorrhage (p = 0.382), age (p = 0.197), midline shift (p = 0.199), or volume of the hemorrhage (p = 0.129, or p = 0.078 if hemorrhages in the cerebellum are excluded). The initial GCS score, however, was associated with an increased risk of death, with lower GCS scores increasing the risk of death (p = 0.041). No patients with an initial GCS score less than 11 survived beyond 30 days. Only 1 patient with an intraparenchymal hemorrhage had intraventricular blood on initial CT, so we were unable to analyze this factor for its association with death.

Figure 1 shows a Kaplan-Meier survival curve for those patients with an LVAD who did not develop an ICH and those who did develop an ICH. There is a significant difference (p = 0.008) in the curves, with those patients who developed an ICH having significantly increased mortality compared with the natural history of patients on LVAD therapy.
The use of LVADs has been increasing as the indications become broader, particularly as a destination therapy. Patients are often treated with antiplatelet and anticoagulation agents while LVADs are in place to reduce the risk of embolic events and pump failure. The use of these agents, however, increases the risk of ICH. As the use of LVADs increases, so too does our exposure to ICHs in patients with LVADs. Few data are available to guide decision making regarding these patients, including which patients are appropriate candidates for operative intervention, how antiplatelet and anticoagulation medications should be managed in these patients, and what prognostic information should be provided to patients and their families. In this study, we sought to examine management and outcomes in LVAD patients to help clinicians faced with this clinical dilemma.

One of the original landmark trials in the use of LVADs was the REMATCH (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure) study. This study showed that patients with advanced heart failure had a survival benefit and increased quality of life when LVADs were used. In that study, neurological events were monitored but ICH specifically was not. In another study, 16% of patients with an LVAD had a stroke. A subsequent study examining placement of a continuous-flow LVAD also monitored for neurological events, but this study specifically monitored for hemorrhagic as well as ischemic strokes. In that study, 3% of patients suffered an ICH. A further study comparing the use of a pulsatile-flow LVAD versus a continuous-flow LVAD showed the rate of ICH to be 11% in the continuous-flow group and 8% in the pulsatile-flow group. In our study, the rate of ICH was 11%, our cohort involving a mix of pulsatile- and continuous-flow pumps

### TABLE 3: Outcomes in patients with an LVAD who developed an ICH

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All</th>
<th>IPH</th>
<th>SDH</th>
<th>SAH</th>
</tr>
</thead>
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<tr>
<td>death at 30 days (%)</td>
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<td>10</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>death at 1 yr (%)</td>
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<td>11</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>median GOS at 6 mos (range)</td>
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<td>1</td>
<td>3.5</td>
<td>5</td>
</tr>
<tr>
<td>median GOS at 1 yr (range)</td>
<td>2</td>
<td>1</td>
<td>3.5</td>
<td>5</td>
</tr>
</tbody>
</table>

* A single patient with an isolated intraventricular hemorrhage is included in the ICH category.

### Discussion

The use of LVADs has been increasing as the indications become broader, particularly as a destination therapy. Patients are often treated with antiplatelet and anticoagulation agents while LVADs are in place to reduce the risk of embolic events and pump failure. The use of these agents, however, increases the risk of ICH. As the use of LVADs increases, so too does our exposure to ICHs in patients with LVADs. Few data are available to guide decision making regarding these patients, including which

![Fig. 1. Kaplan-Meier survival curves for LVAD patients who suffer an ICH and LVAD patients who do not suffer an ICH. Survival is significantly worse in those patients who suffer an ICH compared with the natural history of patients requiring LVAD therapy.](1066/1067.jpg)
Left ventricular assist device–related intracranial hemorrhage

but predominantly the pulsatile-flow type. Thus, our data are in line with previously published data. At this rate and as LVAD use increases, clinicians certainly will increasingly encounter this clinical scenario.

There are no available data on the risk of ischemic events or pump failure in patients with an LVAD when aspirin and warfarin treatment are withheld. Thus, LVAD patients presenting with an ICH pose a clinical dilemma in managing aspirin and warfarin therapy. The clinician must balance the risk of hemorrhage expansion if aspirin or warfarin is not withheld or is reversed against the risk of a thromboembolic event or pump failure occurring if aspirin or warfarin is withheld or is reversed. In our study, aspirin therapy was withheld in 47% of patients and warfarin therapy was withheld in 61% of patients. Platelets were administered in 39% and fresh-frozen plasma was given to reverse warfarin in 61%. No clinically significant thromboembolic events or pump failures were observed. Thus, short-term suspension of aspirin and warfarin seems safe, but certainly patients should be counseled that the risk of thromboembolic events and pump failure exists if these medications are suspended. The optimal duration for suspending these medications also is unclear. The median duration of aspirin suspension was 6 days whereas that for warfarin suspension was 10.5. After resuming aspirin and warfarin treatment, we did not observe rehemorrhage in any patient in whom these medications had been withheld. These data suggest that withholding aspirin for 1 week and warfarin for 10 days is sufficient to reduce the risk of hemorrhage expansion or rehemorrhage while minimizing the risk of thromboembolic events and pump failure. Further data, however, are needed to clearly support these recommendations.

Whether to offer surgical intervention in these patients is a difficult decision. A previous case series of 8 patients, including 1 in whom an intracranial hematoma was evacuated, suggests that noncardiac surgery in patients with an LVAD does not carry significantly increased risk of morbidity and mortality. In our study, 6 patients underwent cranial operations without any intraoperative deaths, although the morbidity or mortality specifically attributable to the operation is difficult to ascertain. This suggests that if operative intervention is found to be beneficial in these patients, it is feasible without significantly increased intraoperative risk. In our study, 6 patients underwent operative intervention (1 for subdural hematoma and 5 for intraparenchymal hemorrhages). The single patient who underwent evacuation of a subdural hematoma tolerated the procedure well and overall had a good functional outcome. However, recommendations based on a single patient are ill advised, and operative intervention should be considered as for any patient with a subdural hematoma.

The STICH (Surgical Treatment for Intracerebral Hemorrhage) trial provides some guidance for operative intervention in the case of intraparenchymal hemorrhage. In this trial, no long-term benefit for surgery versus conservative management could be established. However, patients with LVADs would have been excluded from this study given their severe preexisting comorbidities. In our study, 5 patients underwent operative intervention for intraparenchymal hemorrhages (2 craniotomies for clot evacuation and 3 hemicraniectomies). Patients undergoing operative intervention universally had a poor outcome: 80% died within 60 days. The single surviving patient had a GOS score of 3 (severe disability) at 6 months. Based on our data, it is difficult to recommend operative intervention for these patients, and more data are certainly needed to make definitive recommendations. It is likely that there is bias in our data in that only the most critically ill patients may have undergone operative intervention and there is no information available concerning how the decision to proceed to the operating room was made. Thus, our data suggest that operative intervention is not beneficial, but no definitive conclusions can be drawn from this limited, possibly biased data set.

Conclusions

An ICH is a devastating event for an LVAD patient. Patients with LVADs already have a reduced life expectancy, particularly without undergoing transplantation. The occurrence of an ICH is not an absolute contraindication to transplantation. In fact, 33% of the patients in our study who suffered an ICH subsequently went on to have a transplantation. However, the survival of an LVAD patient who suffers an ICH is further reduced compared with the natural history of patients on LVAD therapy. The Kaplan-Meier curve shown in Fig. 1 demonstrates this reduction in overall survival. However, our study suggests that outcomes are markedly different among traumatic subarachnoid hemorrhages, traumatic subdural hematomas, and spontaneous intraparenchymal hemorrhages. Outcomes were universally good for patients with a traumatic subarachnoid hemorrhage. There was no 30-day mortality and the median GOS score was 5 at both 6 months and 1 year. Outcomes were worse for patients with traumatic subdural hematomas, with a 30-day mortality rate of 13% and a 1-year mortality rate of 38%. The median GOS score at both 6 and 12 months was 3.5 (moderate to severe disability). Outcomes for patients with an intraparenchymal hemorrhage, however, were markedly worse. The 30-day mortality rate was 59%, and the median GOS score at 6 and 12 months was 1 (death). Thus, outcomes for the various types of ICHs differ substantially, and this knowledge provides some guidance for counseling and prognosticating for patients and their families.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Fletcher, Sullivan. Acquisition of data: Wilson, Stetler, Al-Holou. Analysis and interpretation of data: Wilson, Stetler, Al-Holou, Sullivan. Drafting the article: Wilson, Stetler, Al-Holou. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Fletcher. Statistical analysis: Wilson, Al-Holou. Study supervision: Fletcher, Sullivan.
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