**Title:** Inotrope Selection Patterns and Time Interval-based Outcomes after Left Ventricular Assist Device Surgery: Secondary Analysis of a Single-Center Clinical Trial

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**Background:** Patients undergoing left ventricular assist device (LVAD) implantation are at a high risk for early post-implant right heart failure (RHF) and may require inotrope therapy to optimize right ventricular systolic function in the setting of increased venous return following mechanical LV unloading. However, there is significant variation in inotrope subtype (inodilators or inopressors) selection before, during, and after surgery. While variation in selection can be explained by patient, clinician, and institutional-level factors,[1] there is limited evidence to guide decision making, including the risks and benefits of using both or either inotrope subtypes. The purpose of this study is to characterize inotrope subtype selection patterns and describe postoperative outcomes in a subset of LVAD patients enrolled in a previous single-center clinical trial.

**Methods:** We conducted a secondary analysis of the LVAD cohort from the INSPIRE-FLO randomized clinical trial that showed no differences in outcomes when comparing two classes of inhaled pulmonary vasodilators in adult cardiac surgery.[2] First, we identified patterns of inotrope subtype selection, categorized as inodilators (InoD: dobutamine, milrinone), inopressors (InoP: epinephrine, norepinephrine, dopamine) or both (InoB) from the preoperative period through postoperative day (POD) 14. We then grouped time into clinically relevant intervals surrounding LVAD surgery, including preoperative (anytime before surgery incision), intraoperative (from incision to ICU admission), POD 0-2 (early acute), POD 3-7 (late acute), and POD 8-14 (early non-acute) intervals, and identified trajectories of inotrope subtype selection across the time continuum. Inotrope subtypes were determined by use of any InoP or InoD during the specified interval. Finally, we described outcomes by time interval, including post-implant RHF, postoperative acute kidney injury (AKI) by KDIGO criteria, duration of mechanical ventilation, ICU and hospital length of stay (LOS), and mortality, based on inotrope subtype selection within each time interval.

**Results:** One-hundred LVAD patients were included in this analysis (Table 1). Of these, 61 patients received preoperative inotropes (6 InoP, 39 InoD, 16 InoB) and 39 patients did not. (Figure 1). Intraoperatively, all patients received InoP, with 59 receiving InoB. Postoperatively, selection patterns over the 14 days were consistent with reduced InoP and InoB selection while there was growing InoD usage between POD 5-7 and progressive curtailing of all three groups by POD 14 (Figure 1). We found significant heterogeneity in selection patterns across the continuum of inotrope usage with a majority of patients switching between subtypes at some point in the 14-day postoperative period (Figure 2). Finally, we observed potentially important differences in outcomes by inotrope subtypes and time-based intervals (Table 2). For example, amongst the inotrope subtypes, the InoP group displayed the highest AKI rates during the preoperative and intraoperative time interval, whereas AKI was highest in patients in the InoB group postoperatively (Figure 3).

**Conclusions:** In this subset of LVAD patients from the INSPIRE-FLO trial, we found significant variation in pre-operative and post-operative administration of inotrope subtypes. Furthermore, we observed differences in outcomes based on the time interval, such as AKI, post-operatively for patients in each administration group. Future work will incorporate inotrope subtype selection as a time-varying covariate in time-to-event analysis to identify whether patterns in inopressor and inodilator use are significantly associated with patient outcomes.

**References:**

1. Mathis MR et al. Anesthesiology. 2023; 139(2): 122-141. *PMID:37094103, PMCID:PMC10524016*
2. Ghadimi K et al. Circulation. 2023;148(17):1316-1329. *PMID 37401479, PMCID:PMC10615678*
3. Kormos RL et al. J Heart Lung Transplant. 2020; 39(8):735-750. *PMID 32386998*

**Table 1. Baseline Characteristics**

| **Parameter** | **[a]N = 100** |
|---|---|
| **Age, years (Median, IQR)** | 61.5 [50.0, 68.5] |
| **Gender, Male** | 76 |
| **Race** | |
| African American | 44 |
| White | 55 |
| Other | 1 |
| **BMI (Median, IQR)** | 30.1 [25.0, 35.7] |
| **Hypertension** | 79 |
| **COPD** | 25 |
| **Diabetes** | 46 |
| **Liver cirrhosis** | 12 |
| **Asthma** | 6 |
| **Previous Venous thromboembolic disease** | 78 |
| **Atrial fibrillation** | 55 |
| **Home inotropes** | 20 |
| **NYHA class 3 or 4** | 80 |
| **INTERMACS 4-7, Primary LVADs only** | 7 |
| **Previous CABG or Valve surgery** | 29 |
| **Previous sternotomy** | 45 |
| **Previous PCI (N)** | 34 |
| **Pulmonary Hypertension** | |
| Isolated Pre-capillary PH | 5 |
| Isolated Post-capillary PH | 31 |
| Combined PH | 47 |
| **Right heart catheterization** | |
| Cardiac Index, L/min/$m^2$ (Median, IQR) | 1.8 [1.5, 2.2] |
| Right atrial pressure, mmHg (Median, IQR) | 13.0 [9.0, 18.0] |
| Pulmonary vascular resistance, Wood Units (Median, IQR) | 3.2 [1.9, 4.4] |
| Pulmonary capillary wedge pressure, mmHg (Median, IQR) | 24.0 [20.0, 30.5] |
| Mean pulmonary artery pressure, mmHg (Median, IQR) | 35.2 [28.2, 42.7] |
| **Lab values** | |
| Hemoglobin, g/dL (Median, IQR) | 10.9 [9.1, 12.3] |
| Platelets x $10^3/\mu L$ (Median, IQR) | 202.0 [150.5, 248.5] |
| INR (Median, IQR) | 1.3 [1.1, 1.4] |
| aPTT, seconds (Median, IQR) | 67.0 [51.0, 75.1] |
| Creatinine, mg/dL (Median, IQR) | 1.3 [0.9, 1.7] |
| **Chronic kidney disease (Stage)** | |
| 1 | 26 |
| 2 | 25 |
| 3 | 41 |
| 4 | 7 |
| 5 | 1 |
| **Additional procedures** | |
| ASD/PFO closure | 4 |
| Aortic valve | 12 |
| Mitral valve | 2 |

| | |
|---|---|
| Tricuspid valve | 13 |
| **CPB time, Minutes (Median, IQR)** | 122 [79, 174] |
| **Intraoperative transfusions** | |
| Packed red blood cells, ml (Median, IQR), N = 61 | 900 [600, 1400] |
| Fresh frozen plasma, ml (Median, IQR), N = 29 | 980 [600, 1200] |
| Cryoprecipitate, ml (Median, IQR), N =32 | 220 [158.5, 321.5] |
| Platelets, ml (Median, IQR), N = 60 | 476 [299, 689.5] |
| #Randomized to Nitric Oxide (100 – N = #Randomized to Inhaled Epoprostenol) | 48 |

[a]Samples size of 100 patients where sample size/100 is also percentage
aPTT, activated partial thromboplastin time; ASD, atrial septal defect; BMI, body mass index; CPB, cardiopulmonary bypass; COPD, chronic obstructive pulmonary disease; INR, international normalized ratio; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PFO, patent foramen ovale; PH, pulmonary hypertension.

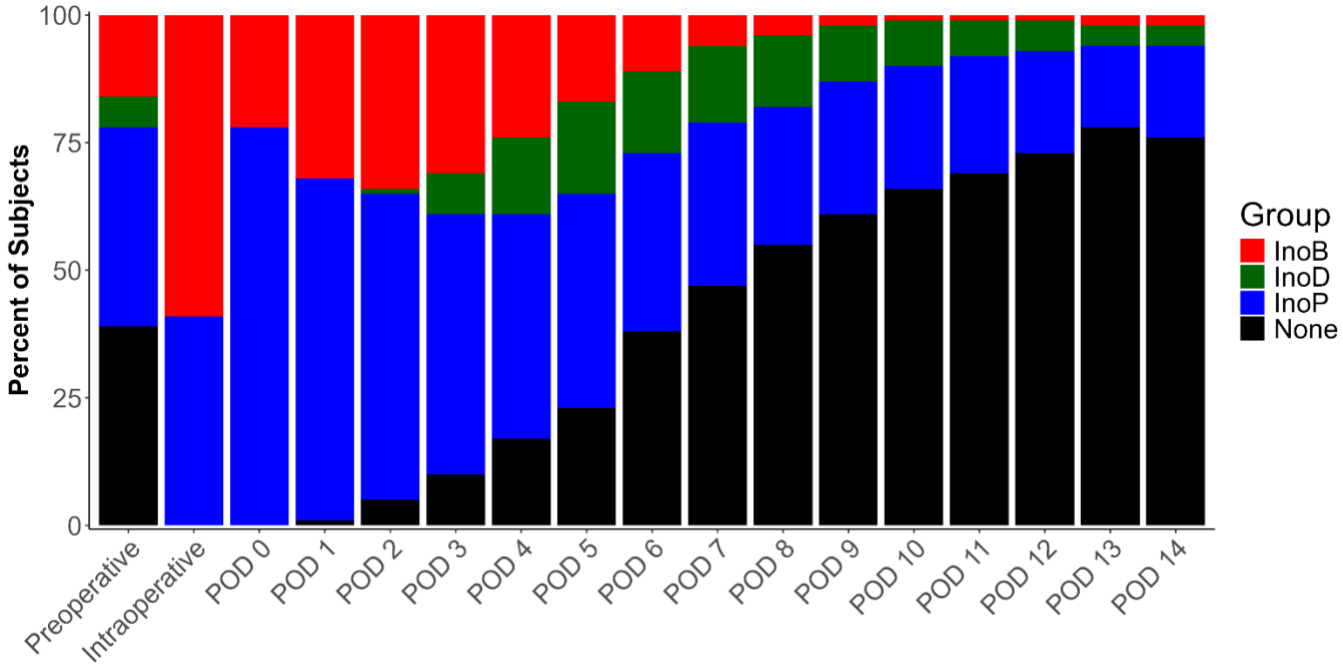


**Figure 1. Inotrope subtype selection before, during, and after LVAD implant surgery through POD 14.** Number of patients receiving inopressors only (InoP), inodilators only (InoD), both inopressors and inodilators (InoB), or no support / discontinued support (None) in the preoperative, intraoperative, and postoperative periods. POD, postoperative day.

**Table 2. Outcomes By Selection Patterns Grouped by Time Period**

| Outcomes | Preoperative | | | Intraoperative | | | POD 0-2 | | | POD 3-7 | | | POD 8-14 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | None (N=39) | InoP (N=6) | InoD (N=39) | Both (N=16) | InoP (N=41) | Both (N=59) | InoP (N=53) | Both (N=47) | None (N=10) | InoP (N=45) | InoD (N=7) | Both (N=38) | None (N=50) | InoP (N=31) | InoD (N=15) | Both (N=4) |
| **90 Day Mortality** | 5 (12.8) | 0 (0) | 6 (15.4) | 1 (6.3) | 5 (12.2) | 7 (11.9) | 6 (11.3) | 6 (12.8) | 1 (10.0) | 6 (13.3) | 0 (0) | 5 (13.2) | 2 (4.0) | 6 (19.4) | 3 (20.0) | 1 (25.0) |
| **Moderate or Severe RHF** | 15 (38.5) | 3 (50.0) | 16 (41.0) | 10 (62.5) | 17 (41.5) | 27 (45.8) | 23 (43.4) | 21 (44.7) | 0 (0) | 24 (53.3) | 1 (14.3) | 19 (50.0) | 1 (2.0) | 27 (87.1) | 12 (80.0) | 4 (100.0) |
| **Post-Implant RHF** | 11 (28.2) | 2 (33.3) | 10 (25.6) | 4 (25.0) | 10 (24.4) | 17 (28.8) | 13 (24.5) | 14 (29.8) | 0 (0) | 16 (35.6) | 0 (0) | 11 (29.0) | 1 (2.0) | 18 (58.1) | 4 (26.7) | 4 (100.0) |
| **AKI** | 28 (71.8) | 5 (83.3) | 29 (74.4) | 12 (75.0) | 31 (75.6) | 43 (72.9) | 35 (66.0) | 39 (83.0) | 4 (40.0) | 33 (73.3) | 5 (71.4) | 32 (84.2) | 31 (62.0) | 25 (80.7) | 14 (93.3) | 4 (100.0) |
| **ICU LOS** | 7 [4, 15] | 7 [3, 32] | 7 [3, 11] | 6 [4, 12] | 7 [4, 13] | 6 [4, 11] | 7 [4, 11] | 6 [4, 14] | 3 [2, 4] | 8 [5, 15] | 4 [2, 7] | 8 [4, 13] | 4 [3, 5] | 11 [7, 18] | 10 [6, 13] | 25 [19, 44] |
| **Hospital LOS** | 18 [14, 35] | 44 [11, 84] | 19 [14, 27] | 22 [17, 31] | 18 [13, 35] | 7 [4, 13] | 20 [14, 31] | 18 [14, 34] | 16 [11, 21] | 20 [15, 27] | 15 [13, 21] | 21 [15, 39] | 15 [12, 19] | 24 [17, 38] | 36 [20, 46] | 50 [30, 116] |
| **Duration of Mechanical Ventilation** | 25 [15, 60] | 31 [11, 70] | 17 [10, 38] | 13 [10, 34] | 25 [10, 56] | 19 [10, 41] | 23 [11, 51] | 17 [10, 38] | 13 [7, 21] | 32 [10, 53] | 9 [4, 11] | 25 [12, 60] | 15 [9, 25] | 39 [14, 85] | 25 [12, 54] | 200 [88, 246] |

Moderate or Severe RHF defined by 2014 INTERMACS criteria. Post-implant RHF defined by updated 2020 INTERMACS criteria. AKI, acute kidney injury; InoP, inopressors; InoD, inodilators; InoB, both; LOS, length of stay; POD, post-operative day; RHF, right heart failure.

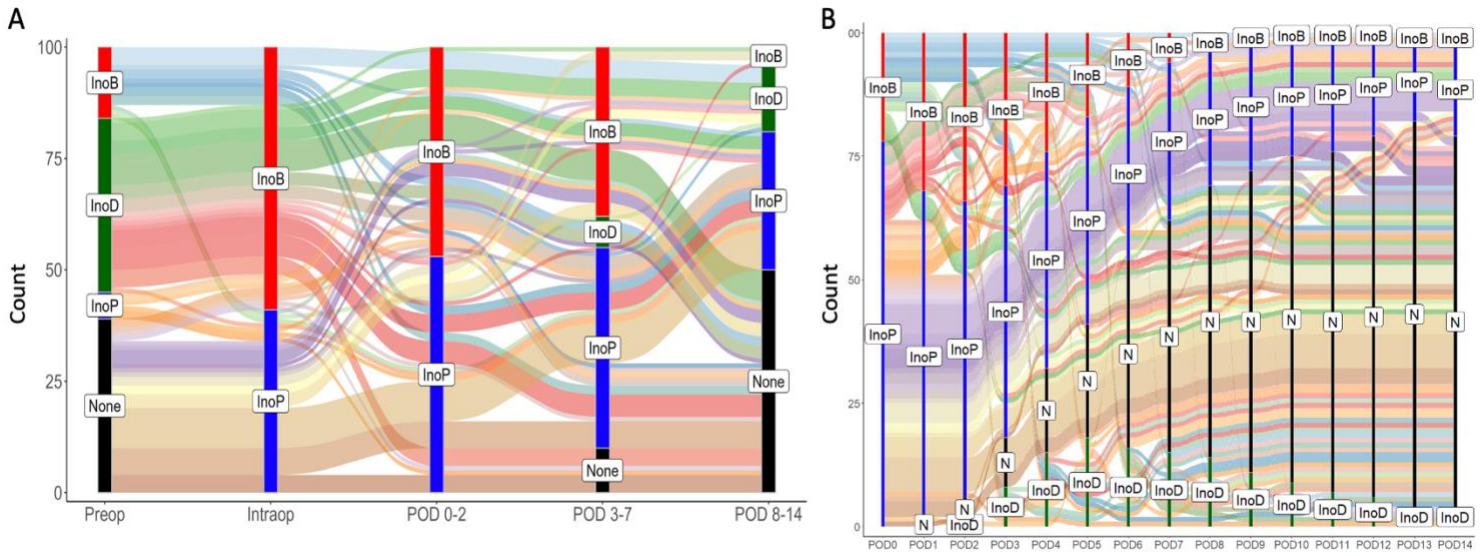


**Figure 2. Inotrope subtype selection patterns over the time continuum of inotrope usage.** Patients were grouped as receiving inopressors only (InoP), inodilators only (InoD), both inopressors and inodilators (InoB), or no inotropes / discontinued inotropes (None). **A.** Selection patterns in the preoperative, intraoperative, POD 0-2, POD 3-7, POD 8-14 time intervals. Each color band represents an individual pattern with 27 total patterns identified in this cohort batched by these time intervals across the continuum of inotrope usage. Preoperative subtype selection includes InoP, InoD, InoB, and none groups, intraoperative and POD 0-2 selection includes InoP and InoB, and POD3-14 subtype selection reintroduces the InoD category along with InoP and InoB categories. **B.** The majority of heterogeneity in inotrope subtype selection was observed in the postoperative period and the daily selection patterns are displayed from POD 0 through POD 14. Each color band represents an individual pattern with 57 total patterns identified in this cohort batched by daily intervals across the continuum of postoperative inotrope usage. POD, postoperative day.

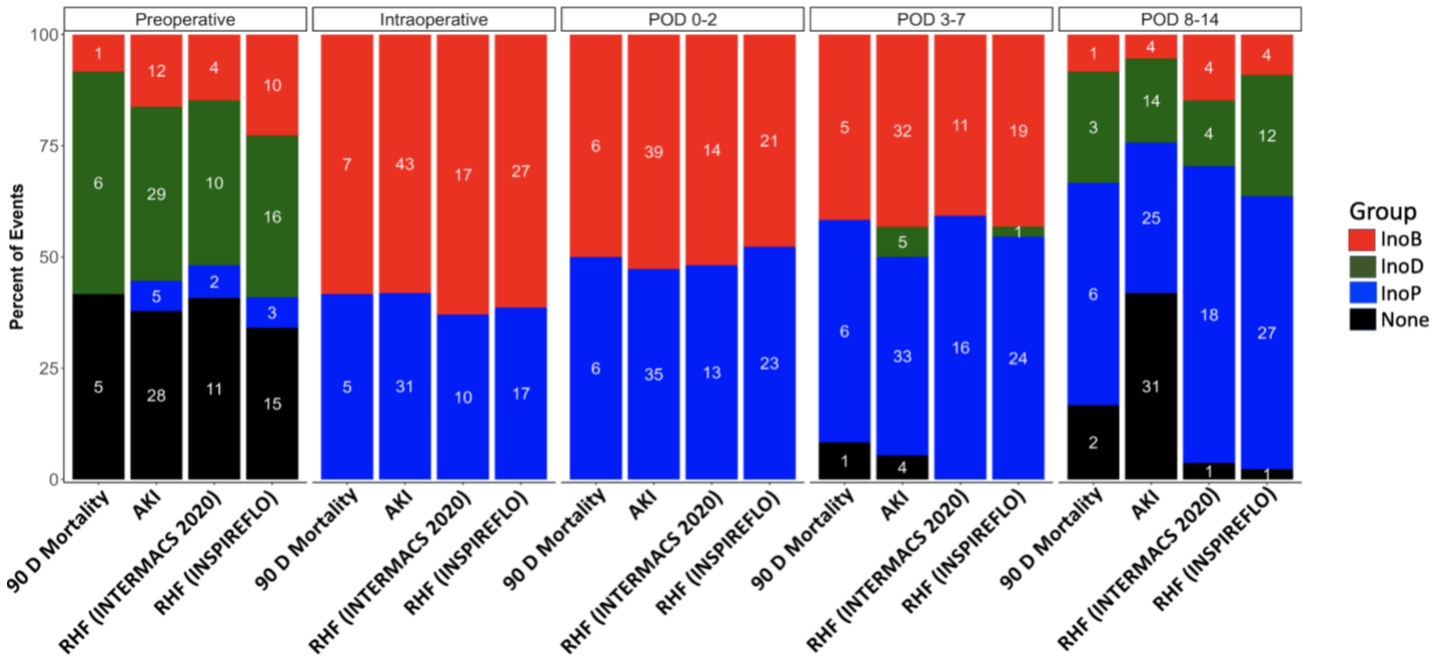


**Figure 3. Inotrope subtype selection patterns and association with time-based outcomes from preoperative to POD14 after LVAD surgery.** Patients were grouped as receiving inopressors only (InoP), inodilators only (InoD), both inopressors and inodilators (InoB), or no inotropes / discontinued inotropes (None). Incidence of outcomes by selection patterns were assessed in the preoperative, intraoperative, POD 0-2, POD 3-7, POD 8-14 time intervals. Percent of events is in relation to the total number of events in each time period. AKI, acute kidney injury; INSPIRE-FLO, Inhaled Selective Pulmonary Vasodilators for Advanced Heart Failure Therapies and Lung Transplantation Outcomes; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; RHF, right heart failure; POD, postoperative day.