


# Association of preoperative duration of inotropy on prevalence of right ventricular failure following LVAD implantation

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## Abstract

**Aims** 20% to 40% of left ventricular assist device (LVAD) device implantations are complicated by right ventricular (RV) failure that results in significant morbidity and mortality. We hypothesized that the duration on milrinone infusion is an independent risk factor for RV failure following LVAD implantation.

**Methods and results** Retrospective demographic, clinical and hemodynamic data were collected on all adults with ACC/AHA stage D heart failure on intravenous milrinone who underwent LVAD implantation between 2012 and 2019. Patients ( $n = 104$ ) were divided into two groups, those on milrinone <30 days (STM,  $n = 55$ ) vs.  $\geq 30$  (LTM,  $n = 49$ ). The primary endpoint was the prevalence of RV failure (need for inotropic support for more than 14 days or RV assist device) within 30 days post-LVAD implantation. There were no significant differences between STM and LTM patients with respect to demographic, echocardiographic, right heart catheterization data, or baseline medications. The mean age of patients was  $55.6 \pm 12$  years (70% male patients). Mean duration on milrinone was 13.7 vs. 81.0 days in STM and LTM, respectively. Forty-five (43.3%) patients developed RV failure. LTM had higher prevalence of RV failure with odds ratio (OR) = 5.04 (95% CI 2.18–11.68,  $P = 0.0002$ ). After adjusting for age, gender, and co-morbidity count, the OR was 6.33 (95% CI 2.51–15.93),  $P < 0.0001$ .

**Conclusions** In this retrospective study of ACC/AHA stage D HF patients, longer duration of milrinone infusion was associated with higher prevalence of RV failure after LVAD implantation.

**Keywords** Heart failure; Left ventricular assist device; Milrinone; Inotropes; Right ventricular failure

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## Introduction

Left ventricular assist device (LVAD) implantation has become a mainstay in the treatment of end-stage heart failure (HF) for several indications, including bridging to cardiac transplantation or as destination therapy.<sup>1</sup> The prevalence of right ventricular (RV) failure post-LVAD implantation has been reported between 20% and 40%, resulting in significant morbidity and mortality. The development of RV failure also shortens survival even after successful heart transplantation in BTT LVAD patients.<sup>2–4</sup> Most

patients in the current era at the time of LVAD implant are on continuous intravenous milrinone to maintain cardiac output and end organ perfusion for a variable duration of time.<sup>5,6</sup> Prior studies have demonstrated inotrope dependency as a predictor for RV failure post-LVAD implant.<sup>7</sup> However, the impact of the duration of inotrope dependency on post-LVAD RV failure has not been studied. We hypothesized that longer duration of inotrope dependency for end-stage HF may have a deleterious effect on RV function and contractile reserve. The objective of this study was to investigate whether longer duration of

milrinone infusion prior to LVAD implantation is associated with a higher prevalence of RV failure post-implantation.

## Methods

The study was a retrospective analysis of data from a single academic centre. Institutional Review Board approval was obtained. We included all adults with ACC/AHA stage D HF patients who were on continuous IV milrinone infusion and underwent continuous-flow LVAD [HeartWare® (HeartWare International Inc, Framingham, MA) or HeartMate II® (Thoratec Corporation, Pleasanton, CA)] implantation at our institution between February 2012 and October 2018. The indications for implantation were bridge to transplant, bridge to candidacy, and destination therapy. We excluded patients who presented with multiorgan failure and/or underwent LVAD implantation on an emergency basis. We also excluded patients who required mechanical circulatory support while awaiting LVAD placement. Patients were divided into two groups, those on milrinone for less than 30 days (STM) vs. more than >30 days (LTM). Of note, patients were not hospitalized for the entire duration on milrinone but were discharged until a decision about surgery was reached and/or work up was completed. Demographic, clinical, laboratory, echocardiographic, and right heart catheterization obtained were the most recent prior to LVAD implantation. RV systolic function was qualitatively described as (in order of severity) normal, or mildly, moderately, markedly, or severely reduced. This assessment was obtained from the echocardiography report and relied on visual assessment by the echocardiography reader. RV end-diastolic diameter was measured in the apical four-chamber view at the base.

During index hospitalization for LVAD surgery, major bleeding was defined as symptomatic bleeding in a critical area or organ, such as retroperitoneal, or pericardial, and/or bleeding leading to transfusion of two or more units of whole blood or red cells. RV failure was defined as requiring RVAD implantation, or requirement of prolonged (>14 days) of inotropic support within 30 days post-LVAD implantation. The primary outcome was the prevalence of RV failure post-LVAD implantation. We compared baseline characteristics of study patients between the two groups based on the duration of milrinone infusion, dichotomized by 30 days, by using  $\chi^2$  test for categorical and t test for continuous variables. Logistic regression model was developed to examine whether milrinone duration was associated with RV failure. Univariate logistic analysis of each demographic, laboratory, catheterization, and echocardiographic variable was calculated. Milrinone duration was treated as continuous and dichotomous separately. Multivariable logistic models were constructed by adjusting for age, gender, and co-morbidity count. Co-morbidities

studied were hypertension, atrial fibrillation, coronary artery disease, cerebrovascular disease, chronic kidney disease, and diabetes mellitus. A second multivariable logistic model adjusted for HbA1c and blood-urea nitrogen based on having a significant univariate test at *P* value cut-off point of 0.10. A third multivariable logistic model adjusted for gender and HbA1c based on backwards stepwise regression initially selecting variables having a univariate test at *P* value cut-off point of 0.25. Results were considered significant for *P* value < 0.05. All analyses were performed with SAS version 9.4 (SAS Institute, Inc).

## Results

A total of 104 patients satisfied the criteria for this study, 55 were in STM group and 49 in the LTM group. Baseline demographic, clinical, laboratory, echocardiographic, right heart catheterization data, and baseline medications are summarized in *Table 1*. The mean age of patients was  $55.6 \pm 12.3$  years; 70% of patients were male patients. The mean duration of follow-up was 27 months. The mean duration on milrinone was  $13.7 \pm 7.4$  days in STM (median: 14.0, IQ range: 7.0–19.0) vs.  $81.0 \pm 48.0$  in LTM (median: 65.0 IQ range: 44.0–105.0). Twenty-eight (50.9%) of patients in STM vs. 35 (71.4%) had hypertension (*P* value = 0.0326). LTM patients had a statistically significant higher cardiac output by Fick method but not by thermodilution. Otherwise, there were no significant differences between STM and LTM patients. Forty-five patients (43.3%) developed RV failure. Baseline characteristics comparison between patients who developed RV failure and those who did not are summarized in *Table 1*. Patients who developed RV failure tended to have a higher glycosylated haemoglobin ( $6.7 \pm 1.3$  vs.  $6.1 \pm 1.2$ , *P* = 0.0172), otherwise, there were no significant differences in the baseline demographic, clinical, laboratory, echocardiographic, and right heart catheterization values between the two groups.

Follow-up duration, LVAD surgical complications and outcomes are summarized in *Table 2*. The mean follow-up duration post-LVAD implantation was  $27.0 \pm 26$  months. During index hospitalization, there were no statistically significant differences between groups in the rates of surgical complications requiring reoperation or other major complications. Following LVAD implantation, 45 (43.3%) patients developed RV failure. Five (9.1%) patients in the STM group vs. 9 (18.4%) in the LTM group needed RVAD support. Nine (16.4%) patients in the STM group vs. 22 (44.9%) in the LTM group needed inotropic support for more than 14 days (*Figure 1*). LTM patients had a significantly higher prevalence of RV failure; odds ratio (OR) = 5.04 (95% CI 2.18–11.68), *P* = 0.0002. When used as a continuous variable, 1 day of milrinone infusion was associated with 1% higher

**Table 1** Patient demographics, and baseline clinical, laboratory, echocardiographic characteristics, and medications

| Characteristics                      | Total (n = 104) | STM (n = 55) | LTM (n = 49) | P value | No RVF (n = 59) | RVF (n = 45) | P value |
|--------------------------------------|-----------------|--------------|--------------|---------|-----------------|--------------|---------|
| Age, year                            | 55.6 ± 12.3     | 55.2 ± 11.5  | 56.1 ± 13.2  | 0.692   | 54.8 ± 11.9     | 56.7 ± 12.8  | 0.437   |
| Male (%)                             | 70 (67.3)       | 36 (65.5)    | 34 (69.4)    | 0.670   | 44 (74.6)       | 26 (57.8)    | 0.070   |
| Ischemic cardiomyopathy (%)          | 39 (37.5)       | 20 (36.4)    | 19 (38.8)    | 0.800   | 20 (33.9)       | 19 (42.2)    | 0.385   |
| LVAD indication                      |                 |              |              | 0.889   |                 |              | 0.056   |
| Destination (%)                      | 42 (40.4)       | 21 (38.2)    | 21 (42.9)    |         | 18 (30.5)       | 24 (53.3)    |         |
| Bridge to transplant (%)             | 51 (49.0)       | 28 (50.9)    | 23 (46.9)    |         | 33 (55.9)       | 18 (40.0)    |         |
| Bridge to candidacy (%)              | 11 (10.6)       | 6 (10.9)     | 5 (10.2)     |         | 8 (13.6)        | 3 (6.7)      |         |
| Duration on milrinone (days)         | 45.4 ± 47.4     | 13.7 ± 7.4   | 81.0 ± 48.0  | <0.001  | 34.8 ± 42.6     | 59.2 ± 50.1  | 0.009   |
| Hypertension (%)                     | 63 (60.6)       | 28 (50.9)    | 35 (71.4)    | 0.033   | 34 (57.6)       | 29 (64.4)    | 0.481   |
| Cerebrovascular disease (%)          | 5 (4.8)         | 1 (1.8)      | 4 (8.2)      | 0.131   | 2 (3.4%)        | 3 (6.7)      | 0.439   |
| Atrial fibrillation (%)              | 38 (36.5)       | 20 (36.4)    | 18 (36.7)    | 0.969   | 22 (37.3)       | 16 (35.6)    | 0.856   |
| Diabetes mellitus (%)                | 44 (42.3)       | 24 (43.6)    | 20 (40.8)    | 0.771   | 21 (35.6)       | 23 (51.1)    | 0.112   |
| Chronic kidney disease (%)           | 36 (34.6)       | 19 (34.6)    | 17 (34.7)    | 0.987   | 18 (30.5)       | 18 (40.0)    | 0.313   |
| End-stage renal disease              | 2 (2.0)         | 1 (1.8)      | 1 (2.0)      | 0.941   | 0               | 2 (4.4)      | 0.118   |
| Previous CABG (%)                    | 16 (15.4)       | 5 (9.1)      | 11 (22.4)    | 0.0658  | 6 (10.2)        | 10 (22.2)    | 0.347   |
| Previous valve surgery (%)           | 8 (7.7)         | 3 (5.4)      | 5 (10.2)     | 0.358   | 6 (10.2)        | 2 (4.4)      | 0.273   |
| INTERMACS Profile, (%)               |                 |              |              |         |                 |              |         |
| 2                                    | 33 (31.7)       | 17 (30.9)    | 16 (32.6)    | 0.915   | 17 (28.8)       | 14 (35.6)    | 0.513   |
| 3                                    | 57 (54.8)       | 29 (52.7)    | 28 (57.1)    |         | 37 (62.7)       | 30 (66.7)    |         |
| 4                                    | 5 (4.8)         | 2 (1.9)      | 3 (6.1)      |         | 3 (5.1)         | 1 (7.7)      |         |
| Laboratory values                    |                 |              |              |         |                 |              |         |
| Total bilirubin, mg/dL               | 1.1 ± 1.4       | 1.2 ± 1.7    | 1.0 ± 0.9    | 0.481   | 1.0 ± 0.7       | 1.2 ± 1.9    | 0.535   |
| Creatinine, mg/dL                    | 1.3 ± 0.6       | 1.3 ± 0.7    | 1.4 ± 0.4    | 0.827   | 1.3 ± 0.7       | 1.4 ± 0.5    | 0.711   |
| Blood-urea nitrogen, mg/dL           | 25.1 ± 15.0     | 23.1 ± 14.2  | 27.2 ± 15.7  | 0.169   | 22.9 ± 15.6     | 27.9 ± 13.8  | 0.095   |
| AST (U/L)                            | 37.6 ± 39.3     | 42.1 ± 44.1  | 32.4 ± 32.6  | 0.212   | 41.3 ± 49.8     | 32.9 ± 18.2  | 0.283   |
| ALT (U/L)                            | 33.3 ± 36.2     | 35.3 ± 32.9  | 29.8 ± 39.7  | 0.367   | 32.6 ± 32.9     | 34.1 ± 40.4  | 0.842   |
| Albumin (g/L)                        | 3.7 ± 0.6       | 3.6 ± 0.8    | 3.7 ± 0.4    | 0.569   | 3.7 ± 0.7       | 3.7 ± 0.5    | 0.901   |
| HBA1C (%)                            | 6.4 ± 1.2       | 6.5 ± 1.2    | 6.2 ± 1.3    | 0.361   | 6.1 ± 1.2       | 6.7 ± 1.3    | 0.017   |
| Haemoglobin (g/dL)                   | 11.0 ± 1.8      | 11.1 ± 1.8   | 11.0 ± 1.7   | 0.643   | 10.9 ± 1.9      | 11.2 ± 1.7   | 0.381   |
| INR                                  | 1.33 ± 0.41     | 1.32 ± 0.47  | 1.34 ± 0.35  | 0.876   | 1.28 ± 0.34     | 1.34 ± 0.37  | 0.651   |
| Right heart catheterization          |                 |              |              |         |                 |              |         |
| Mean RA pressure                     | 11.4 ± 6.2      | 11.3 ± 6.4   | 11.4 ± 5.9   | 0.939   | 11.1 ± 6.6      | 11.8 ± 5.5   | 0.582   |
| PA systolic                          | 52.4 ± 14.9     | 52.3 ± 15.2  | 52.6 ± 14.8  | 0.917   | 51.8 ± 16.5     | 53.2 ± 12.8  | 0.633   |
| PA diastolic                         | 25.9 ± 9.1      | 26.4 ± 9.0   | 25.3 ± 9.2   | 0.540   | 25.5 ± 9.6      | 26.4 ± 8.5   | 0.627   |
| Mean PA pressure                     | 36.2 ± 10.9     | 36.5 ± 10.8  | 36.0 ± 11.1  | 0.833   | 35.7 ± 11.8     | 37.0 ± 9.6   | 0.537   |
| PCWP                                 | 23.3 ± 8.6      | 23.2 ± 8.8   | 23.4 ± 8.5   | 0.903   | 23.0 ± 9.4      | 23.8 ± 7.6   | 0.645   |
| CO (TD), litres/min                  | 3.9 ± 1.2       | 3.7 ± 1.3    | 4.0 ± 1.2    | 0.168   | 3.8 ± 1.3       | 3.9 ± 1.2    | 0.707   |
| CI (TD), litres/min/m <sup>2</sup>   | 1.9 ± 0.5       | 1.9 ± 0.6    | 1.9 ± 0.5    | 0.624   | 1.9 ± 0.6       | 1.9 ± 0.5    | 0.961   |
| CO (Fick), litres/min                | 3.8 ± 1.2       | 3.5 ± 1.2    | 4.1 ± 1.2    | 0.012   | 3.7 ± 1.2       | 3.9 ± 1.3    | 0.455   |
| CI (Fick), litres/min/m <sup>2</sup> | 1.9 ± 0.5       | 1.8 ± 0.5    | 2.0 ± 0.4    | 0.032   | 1.8 ± 0.5       | 1.9 ± 0.4    | 0.657   |
| PAPi                                 | 3.6 ± 3.3       | 3.9 ± 4.0    | 3.3 ± 2.4    | 0.318   | 4.0 ± 3.9       | 3.2 ± 2.3    | 0.255   |
| CVP/PCWP                             | 0.5 ± 0.2       | 0.5 ± 0.3    | 0.5 ± 0.2    | 0.991   | 0.5 ± 0.3       | 0.5 ± 0.2    | 0.884   |
| TTE indices                          |                 |              |              |         |                 |              |         |
| Ejection fraction                    | 18.5 ± 5.3      | 18.0 ± 4.6   | 19.0 ± 6.0   | 0.311   | 18.2 ± 4.9      | 18.8 ± 5.9   | 0.568   |
| RV systolic dysfunction              |                 |              |              | 0.515   |                 |              | 0.647   |
| None (%)                             | 21 (20.2)       | 10 (18.2%)   | 11 (22.5)    |         | 14 (23.7)       | 7 (15.6)     |         |
| Mild (%)                             | 32 (30.8)       | 16 (29.1)    | 16 (32.7)    |         | 19 (32.2)       | 13 (28.9)    |         |
| Moderate (%)                         | 32 (30.8%)      | 16 (29.1)    | 16 (32.7)    |         | 16 (27.1)       | 16 (35.6)    |         |
| Severe (%)                           | 19 (18.3)       | 13 (23.6)    | 6 (12.2)     |         | 10 (17.0)       | 9 (20.0)     |         |
| Estimated PASP                       | 46.4 ± 12.4     | 46.9 ± 14.1  | 45.9 ± 10.5  | 0.730   | 46.7 ± 12.9     | 46.0 ± 12.0  | 0.819   |
| RV dilation                          |                 |              |              | 0.288   |                 |              | 0.627   |
| None (%)                             | 12 (19.1)       | 8 (23.5)     | 4 (13.8)     |         | 9 (22.5)        | 3 (13.0)     |         |
| Mild (%)                             | 10 (15.9)       | 5 (14.7)     | 5 (17.2)     |         | 6 (15.0)        | 4 (17.4)     |         |
| Moderate (%)                         | 11 (17.5)       | 8 (23.5)     | 3 (10.3)     |         | 8 (20.0)        | 3 (13.0)     |         |
| Severe (%)                           | 30 (47.6)       | 13 (38.2)    | 17 (58.6)    |         | 17 (42.5)       | 13 (56.5)    |         |
| Medications, n (%)                   |                 |              |              |         |                 |              |         |
| Beta blocker                         | 65 (62.5)       | 38 (69.1)    | 27 (55.1)    | 0.143   | 40 (67.8)       | 25 (55.6)    | 0.205   |
| ACEI/ARB                             | 66 (63.5)       | 34 (61.8)    | 32 (65.2)    | 0.721   | 35 (59.5)       | 31 (58.8)    | 0.943   |
| Nitrates                             | 19 (18.3)       | 10 (18.2)    | 9 (18.4)     | 0.979   | 11 (18.6)       | 8 (17.8)     | 0.917   |
| Hydralazine                          | 18 (17.3)       | 8 (14.5)     | 10 (20.4)    | 0.429   | 7 (11.9)        | 11 (24.4)    | 0.097   |
| Digoxin                              | 14 (13.5)       | 10 (18.2)    | 4 (8.2)      | 0.138   | 9 (15.3)        | 5 (11.1)     | 0.536   |
| Thiazide or loop diuretic            | 101 (97.1)      | 52 (94.6)    | 49 (100)     | 0.913   | 56 (94.9)       | 44 (97.8)    | 0.091   |
| Aldosterone antagonist diuretic      | 49 (47.1)       | 27 (49.1)    | 22 (44.9)    | 0.67    | 25 (42.4)       | 24 (53.3)    | 0.27    |
| Amiodarone                           | 30 (28.8)       | 13 (23.6)    | 17 (34.7)    | 0.215   | 13 (22.0)       | 17 (37.8)    | 0.08    |
| Aspirin                              | 66 (63.5)       | 35 (63.3)    | 31 (63.3)    | 1.0     | 35 (59.3)       | 31 (68.7)    | 0.327   |
| Antiplatelets other than aspirin     | 12 (11.5)       | 9 (16.3)     | 3 (6.1)      | 0.105   | 7 (11.8)        | 5 (11.1)     | 0.912   |

(Continues)

Table 1 (continued)

| Characteristics           | Total (n = 104) | STM (n = 55) | LTM (n = 49) | P value | No RVF (n = 59) | RVF (n = 45) | P value |
|---------------------------|-----------------|--------------|--------------|---------|-----------------|--------------|---------|
| Warfarin                  | 32 (30.8)       | 13 (38.2)    | 19 (38.8)    | 0.95    | 16 (27.1)       | 15 (33.3)    | 0.495   |
| Novel oral anticoagulants | 19 (18.3)       | 11 (5.4)     | 8 (16.3)     | 0.072   | 10 (16.9)       | 10 (22.2)    | 0.499   |
| Dobutamine                | 4 (3.8)         | 1 (1.8)      | 3 (6.1)      | 0.256   | 1 (1.7)         | 4 (8.9)      | 0.091   |

CI, cardiac index; CO, cardiac output; CVP, central venous pressure; INR, international normalized ratio; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVAD, left ventricular assist device; PA, pulmonary artery; PAPI, pulmonary artery pulsatility index; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RA, right atrial; RVEDP, right ventricular end-diastolic pressure; RVF, right ventricular failure; RVSP, right ventricular systolic pressure; TTE, transthoracic echocardiogram. Data are presented as mean  $\pm$  standard error values or as number of patients. Hemodynamic measurements are in mmHg unless stated otherwise

likelihood of developing RV failure in the unadjusted model (OR 1.01, 95% CI:1.00–1.02,  $P = 0.0135$ ). In the first multivariable logistic model, after adjusting for age, gender, and clinically relevant co-morbidities, patients in the LTM group had statistically significant association with RV failure, OR = 6.33 (95% CI 2.51–15.93),  $P < 0.0001$ . In the second multivariable logistic model, after adjusting for HbA1c and blood-urea nitrogen, the OR 7.30 (95%CI 2.72–19.65),  $P$  value  $< 0.001$ . Similar results were obtained from the third multivariable logistic model, after adjusting for gender and HbA1c based on backwards stepwise regression, OR = 8.54 (95%CI 3.02–24.17),  $P$  value  $< 0.001$ . The univariate and multivariate model results are included in *Table 3*. Survival at the end of the follow-up period was 74% ( $n = 77$ ); 15 (27.3%) patients in the STM group vs. 12 (24.5%) in the LTM group ( $P$  value = 0.7466) were non-survivors. Patients with RV failure had significantly higher mortality compared with those without RV failure [(18(40%) vs. 9 (22.5%),  $P$  value = 0.004 3).

## Discussion

This was a retrospective study of the association of milrinone duration prior to LVAD implantation on the prevalence of RV failure post-LVAD implant. In this analysis, we showed longer duration of milrinone infusion prior to LVAD implant was significantly associated with higher prevalence of RV failure after LVAD implantation.

Up to 20% to 40% of LVAD implantations are complicated by RV failure, which results in significant morbidity and mortality.<sup>4,8–10</sup> RV failure frequently necessitates prolonged intensive care unit stays, and in some cases, necessitates RV assist device (RVAD) implantation.<sup>2,7,11,12</sup> Severe refractory RV failure that requires RVAD support portends an even poorer prognosis and has been identified as the most significant risk factor for death after LVAD implantation.<sup>3</sup> The aetiology of RV failure following LVAD implant is unclear and likely multifactorial. Despite the development of numerous risk scores, ability to predict RV failure remains poor.<sup>7</sup> Several risk scores exist which incorporate predictors in the perioperative period include hemodynamic and

echocardiographic parameters such as RV stroke work index  $< 250$ , right atrial pressure  $> 15$  mmHg, severe RV dysfunction on echocardiogram, renal insufficiency, hepatic dysfunction, elevated pulmonary vascular resistance, and reduced tricuspid annular plane systolic excursion (TAPSE  $< 0.75$  cm).<sup>2,7,12–15</sup> In our cohort, most of the known predictors were not significantly correlated with RV failure post-LVAD. This is likely because of the relatively smaller size of the cohort in this study. This also points out the lack of strong risk predictors of post-LVAD RV failure.<sup>10,11</sup>

Initial studies of milrinone in acute HF showed a reduction in re-hospitalization frequency and improvement in HF symptoms.<sup>16</sup> However, studies evaluating long-term infusion of milrinone showed significant adverse outcomes. In The Outcomes of Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF), milrinone was significantly associated with sustained hypotension and atrial arrhythmias compared with placebo.<sup>6</sup> A post hoc analysis showed that intravenous milrinone (0.5  $\mu$ g/kg/min without a loading dose) was associated with higher mortality and re-hospitalization rate in ischemic cardiomyopathy patients. A neutral beneficial effect was seen in patients with non-ischemic cardiomyopathy as the aetiology for decompensated HF.<sup>17</sup> Similarly, the Acute Decompensated Heart Failure National Registry (ADHERE) study also showed a significantly higher in-hospital mortality in patients admitted with acute decompensated HF, when treated with milrinone or dobutamine compared with intravenous nitroglycerine or nesiritide.<sup>18</sup> Subsequently, a meta-analysis of 21 randomized trials also showed that phosphodiesterase inhibitors are associated with significantly higher mortality and cardiac arrhythmias when compared with placebo.<sup>19</sup> Several possible explanations for the deleterious effects of phosphodiesterase inhibitors on mortality have been proposed, including: (i) an excessive increase of intracellular cyclic adenosine monophosphate (cAMP), which decreases in chronic HF patients, possibly as an adaptive response; (ii) an arrhythmogenic effect; or (iii) a potentiation of the deleterious effects of phosphodiesterase inhibitors by concomitant treatment with vasodilators.<sup>19–22</sup>

Among LVAD patients, Drakos *et al.* studied 175 patients who underwent LVAD implantation from 1993 to 2008. Seventy-seven (44%) developed RV failure. Inotrope

Table 2 Patient follow-up, post-surgical complications, and outcomes

| Characteristics  | Total (n = 104) | STM (n = 55) | LTM (n = 49) | P value | No RVF (n = 59) | RVF (n = 45) | P value |
|--|-----------------|--------------|--------------|---------|-----------------|--------------|---------|
| <b>Follow-up</b>   |                 |              |              |         |                 |              |         |
| Duration of follow-up post-LVAD (months)                 | 27.0 ± 26.2     | 30.4 ± 28.5  | 23.2 ± 23.0  | 0.161   | 29.9 ± 27.3     | 23.3 ± 24.4  | 0.205   |
| Heart transplant   | 35 (33.7)       | 18 (32.7)    | 17 (34.7)    | 0.832   | 24 (40.7)       | 11 (24.4)    | 0.083   |
| Duration on LVAD support (days till transplant or death) | 16.8 ± 19.8     | 17.1 ± 20.8  | 16.4 ± 18.7  | 0.859   | 18.6 ± 21.7     | 14.4 ± 16.9  | 0.295   |
| <b>Post-surgical complications (%)</b>                   |                 |              |              |         |                 |              |         |
| Technical complications requiring reoperation            | 12 (11.5)       | 8 (14.5)     | 4 (8.2)      | 0.318   | 5 (8.5)         | 7 (15.6)     | 0.264   |
| Cerebrovascular accident                                 | 1 (1.0)         | 0            | 1 (2.0)      | 0.294   | 0               | 1 (2.2)      | 0.255   |
| Major gastrointestinal bleed                             | 6 (5.8)         | 1 (1.8)      | 5 (10.2)     | 0.068   | 3 (5.1)         | 3 (6.7)      | 0.731   |
| Major bleed, other than GI                               | 3 (2.9)         | 0            | 3 (6.1)      | 0.064   | 1 (1.7)         | 2 (4.4)      | 0.416   |
| Need for haemodialysis or CRRT                           | 5 (4.8)         | 4 (7.3)      | 1 (2.0)      | 0.209   | 2 (3.4)         | 3 (6.7)      | 0.439   |
| <b>Mortality</b>   | 27 (26.0%)      | 15 (27.3%)   | 12 (24.5%)   | 0.747   | 9 (15.3%)       | 18 (40.0%)   | 0.004   |

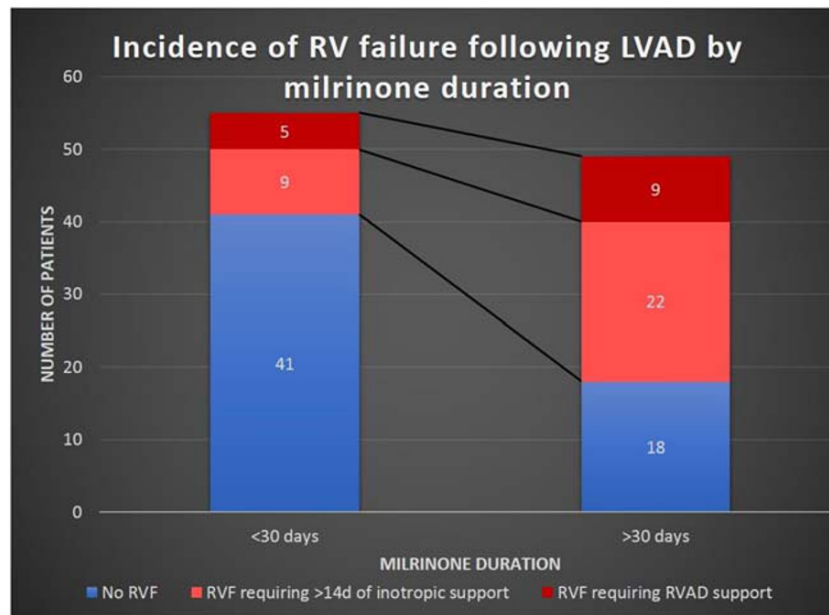
CRRT, continuous renal replacement therapy; LVAD, left ventricular assist device; LTM, left ventricular assist device; RVF, right ventricular failure.

dependency was associated with a higher likelihood with RV failure post-LVAD (OR = 2.45, *P* value = 0.08) and was included in the Drakos score for predicting RV failure.<sup>7</sup> The association of the duration on inotropic support prior to LVAD has never been studied. In our study, we showed a strong correlation between the duration on milrinone and the prevalence of RV failure post-LVAD. In addition to the adverse effects of long-term milrinone described above, we believe that a continuous infusion of inotropic agents for a prolonged period before LVAD implantation might induce tolerance, resulting in a less efficacious response when challenged with inotropes intraoperative or early postoperative period resulting in worsening RV function and RV failure.<sup>23–25</sup>

The results of our study should be interpreted with caution. This was a retrospective study with all the inherent limitations of this research methodology. Although, there were no significant differences in baseline clinical characteristics, echocardiographic and invasive data between the two groups, unmeasured factors might have led some patients to be on longer duration of milrinone. Also, the pathophysiology of patients' HF might have changed since echocardiographic or cardiac catheterization studies were obtained. These changes might have been masked by milrinone administration. Parameters that were included in our multivariate analysis had less than 2% of missing data. However, we did not include some echocardiographic parameters which showed some correlation to RV failure due to the significant number of missing data, that is, tricuspid annulus posterior systolic excursion (TAPSE), RV longitudinal myocardial velocity (*S'*) and fractional area shortening. Further studies are needed to validate this finding in a larger group of patients, ideally in a randomized fashion to eliminate any confounding factors, which are unaccounted for in this study.

There are obvious implications for patients with advanced HF requiring continuous inotropic support and are being considered for advanced HF therapies. The work up for those patients should be expediated to mitigate the risk of RV failure associated with the longer use of inotropes. Duration on intravenous milrinone should be included when risk stratifying patients for RV failure following LVAD implantation surgery. Expediating LVAD workup and implantation for inotrope-dependent patients, mitigates the risk of RV failure, compared with the current practice which could oversee the additional risk from longer periods on inotropic support.

In conclusion, patients who were on LTM had much higher odds of developing RV failure post-LVAD compared with those on STM. Each day on continuous milrinone infusion was independently associated with 1% higher odds of developing RV failure.

**FIGURE 1** Incidence of right ventricular failure following LVAD by milrinone duration.**Table 3** Univariate and multivariable logistic regression models of factors predicting right ventricular failure following LVAD implantation

| Model               | Univariate        |         | Multivariable 1   |         | Multivariable 2   |         | Multivariable 3   |         |
|---------------------|-------------------|---------|-------------------|---------|-------------------|---------|-------------------|---------|
|                     | OR (95% CI)       | P value | OR (95% CI)       | P value | OR (95% CI)       | P value | OR (95% CI)       | P value |
| Milrinone duration  |                   | 0.0002  |                   | <.0001  |                   | <.0001  |                   | <.0001  |
| ≤30 days            | Ref               |         | Ref               |         | Ref               |         | Ref               |         |
| >30 days            | 5.04 (2.18–11.68) |         | 6.33 (2.51–15.93) |         | 7.30 (2.72–19.65) |         | 8.54 (3.02–24.17) |         |
| Age                 | 1.01 (0.98–1.05)  | 0.433   | 1.01 (0.98–1.05)  | 0.442   |                   |         |                   |         |
| Gender              |                   | 0.073   |                   | 0.015   |                   |         |                   | 0.033   |
| Female              | Ref               |         | Ref               |         |                   |         | Ref               |         |
| Male                | 0.47 (0.20–1.07)  |         | 0.30 (0.11–0.79)  |         |                   |         | 0.33 (0.12–0.91)  |         |
| Co-morbidity count  | 1.35 (0.93–1.95)  | 0.115   | 1.54 (1.00–2.37)  | 0.051   |                   |         |                   |         |
| HBA1C               | 1.51 (1.06–2.15)  | 0.023   |                   |         | 1.86 (1.19–2.90)  | 0.006   | 1.95 (1.23–3.08)  | 0.004   |
| Blood-urea nitrogen | 1.02 (1.00–1.05)  | 0.101   |                   |         | 1.00 (0.97–1.04)  | 0.833   |                   |         |

RVF, right ventricular failure

Multivariable model 1: milrinone duration adjusted by age, gender, and co-morbidity based on clinic decision; Multivariable model 2: based on statistically significant variables using  $P < 0.10$  as the cut-off of significance; Multivariable model 3: based on backwards stepwise regression initially selecting variables having a univariate test  $P < 0.25$ .

## Conflict of interest

None declared.

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