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Does Size Matter for Female Continuous-flow LVAD Recipients? A Translational Approach to a Decade Long Question

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Females have increased risk of right-ventricular failure (RVF) and 3 month mortality after left-ventricular assist device (LVAD) implantation. In this translational study, we tested the hypothesis that sex differences in outcomes are driven by pump-induced LV size-volume mismatch, due to a negative impact on interventricular septal (IVS) interdependence. Adult continuous-flow LVAD recipients from the International Society For Heart And Lung Transplantation Mechanically Assisted Circulatory Support registry (n = 15,498) were studied to determine association of female sex with outcomes of 3 month mortality and RVF. Female sex was associated with smaller preimplant left-ventricular end-diastolic diameter (6.5 *vs.* 6.9 cm, $p < 0.001$), increased 3 month mortality (odds ratio [OR]: 1.42, $p < 0.001$) and RVF (OR: 1.18, $p = 0.005$). Smaller left-ventricular end-diastolic diameter was associated with worse outcomes after LVAD implantation (OR for mortality: 1.20, $p < 0.001$; RVF: 1.09, $p < 0.001$), and attenuated the association of female sex with these outcomes. In test bench heart phantoms (n = 4), the IVSs of smaller hearts demonstrated abnormal leftward shift earlier than larger hearts (volume change at IVS shift: 40 [95% confidence interval: 30–52] *vs.* 50 [95% confidence interval: 48–69] ml). Smaller LV size partially mediates worse post-LVAD outcomes for female patients, due to lower volume thresholds for adverse IVS shifting. *ASAIO Journal* XXX; XX;00–00

Key Words: left-ventricular assist device, sex differences, mortality, right-ventricular failure

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Prior analyses of large international registries have demonstrated that females have an increased risk of postoperative right-ventricular failure (RVF) and early 3 month mortality after continuous-flow (CF) left-ventricular assist device (LVAD) implantation; however, the underlying mechanisms are unclear.[1–3] A recent analysis suggests that smaller baseline (preimplant) left-ventricular end-diastolic diameter (LVEDD) in women may mediate a portion of this increased risk.[2,3] We hypothesize that LVAD-induced LV size-volume mismatch amplified by smaller baseline LV cavity sizes in females *versus* males results in adverse hemodynamic consequences of earlier leftward shifting of the interventricular septum (IVS), thereby contributing to the observed sex differences in outcomes post-LVAD.

Leftward IVS displacement occurs secondary to excessive LVAD support leading to a disproportionate reduction in LV volume and filling pressures and from RV pressure or volume overload.[4–7] Excessive septal shift can increase wall stress due to an increase in RV diameter (La-Place's law, wall stress α [Ventricular pressure*radius]/Wall thickness).[4,8] Increased RV wall stress can reduce contraction efficiency, leading to worsening tricuspid regurgitation, reduced RV stroke work, and RVF.[6] In addition, ventricular arrhythmias, severe LVAD preload reduction, hemolysis, thrombus formation, and myocardial injury can occur if the IVS contacts the LVAD cannula.[9–12]

Experimental approaches are useful to study the effect of LVAD support on LV and RV hemodynamics.[13,14] Advancements in additive manufacturing now allow testing in multiple patient-specific heart phantoms.[13,14] Specifically, an ultrasonic sensor can be used in an *in vitro* setting to accurately determine IVS positioning over a range of experimental LV unloading conditions.[13,14] In this proof-of-concept translational research study, we examine (1) clinical data from the International Society for Heart and Lung Transplantation Mechanically Assisted Circulatory Support (IMACS) registry to determine whether baseline (preimplant) LVEDD mediates increased risk of early mortality and postoperative RVF in females, and (2) experimental data generated from biventricular heart phantoms to study the influence of different LV unloading conditions on LV size, volume, and IVS positioning.

Materials and Methods

Clinical Perspective

Database. We utilized deidentified patient-level data from the IMACS Registry,[15] which collects data from patients undergoing durable LVAD support in 35 countries across the globe. Sources of data for the registry include four large collectives: Interagency Registry for Mechanical Circulatory Support (INTERMACS, USA), European Registry for Patients with Mechanical Circulatory Support (EUROMACS, Europe),

Japanese Registry for Mechanical Assisted Circulatory Support (Japan), and the United Kingdom Registry. In addition, 24 hospitals from Australia, Brazil, Colombia, Spain, Finland, Greece, Hong Kong, Ireland, Israel, Italy, Republic of Korea, New Zealand, Saudi Arabia, Singapore, Slovakia, Sweden, and Turkey provide data directly to the Registry. Data are uploaded yearly and merged into the registry for analysis. Single-country, single-collective, device brand, and race data are not available for analysis. This paper was reviewed and approved by the IMACS Steering Committee, and considered exempt from review by the Stanford and Emory University Institutional Review Boards.

Patient population. Adults (≥18 years) who received CF LVAD from January 9, 2013, to September 30, 2017, were included in the study.

Outcomes. Outcomes of interest included 3 month postoperative mortality (censored at transplant, explant or last date of follow-up: October 31, 2017) and postoperative RVF (defined as RVAD requirement and/or ≥14 days of inotropic support post-LVAD).[16]

Statistical analysis. Data are presented as mean ± standard deviation, median (interquartile range [IQR]), or as number (%) of patients. The differences between males and females were examined using two-sample *t*-test for normally distributed continuous variables, Mann–Whitney *U*-test for nonnormally distributed continuous variables, and χ^2 test for categorical variables.

The association of female sex with the post-LVAD outcomes was examined using multivariable binary logistic regression adjusting for all baseline covariates that were significantly different ($p < 0.05$) between males and females (Table 1) with and without LVEDD in the models. Attenuation of the β-estimate due to LVEDD was estimated as $(\beta\text{-estimate}_{\text{without LVEDD in model}} - \beta\text{-estimate}_{\text{with LVEDD in model}})/\beta\text{-estimate}_{\text{without LVEDD in model}}$. Baseline multivariable model covariates were chosen based on prior literature examining sex differences in post-LVAD outcomes,[17–19] and included: age, body surface area (BSA), body mass index, device strategy (bridge to transplant *versus* Destination therapy *versus* bridge to recovery), etiology of HF (ischemic *versus* nonischemic), pump type (centrifugal *versus* axial flow), cardiogenic shock at implant (INTERMACS profiles 1 and 2 *versus* profiles 3–7), serum sodium, blood urea nitrogen, total bilirubin, international normalized ratio, hemoglobin, white blood cell count, serum albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), estimated glomerular filtration rate (eGFR), categorized according to chronic kidney disease stage,[20] right atrial pressure, pulmonary artery diastolic pressure, and cardiac index (CI). There was less than 20% data missingness for all covariates with the exception of CI which had 22% missing data. Missing data were imputed to the median for males and females. A sensitivity subgroup analysis was conducted by median BSA (2.03 m^2).

Experimental Perspective

Test bench. The experimental approach featured a test bench with four biventricular patient-specific silicone heart phantoms. An ultrasound transducer was positioned inside the LV cavity of each phantom and scanned 156 positions on the septal wall using an intricate mirror including a variable elevation and rotation angle (Figure 1A) equivalent to a probe with 156 individual transducers.

Heart phantoms. Four silicone patient-specific heart phantoms were created from gated cardiac computed tomography-derived measurements obtained at end-diastole. Heart models were manufactured using a lost-wax molding technique resulting in a highly accurate representation of the papillary muscles and trabeculation. Talcum powder infused in the silicone mimicked the ultrasonic scattering properties of native myocardium.

Smaller hearts were represented by heart phantoms with LVEDDs of 6.1 and 6.3 cm, and larger hearts by heart phantoms with LVEDDs of 8.1 and 8.3 cm (Figure 1B).[13] A simplified sphericity index was computed for each cardiac phantom at baseline as the ratio of the LV short-axis diameter to the LV long-axis diameter, with larger numbers indicating a more spherical LV.

Curvature calculation. The 156 data points obtained from the ultrasound transducer informed a third-degree polynomial fit per rotation angle α ($p_\alpha(z)$), where z is the height of the ventricle.[13] We estimated the vertical curvatures of each α-segment of the IVS as follows:

$$\kappa_\alpha = \frac{\frac{d^2}{dz^2} p_\alpha(z)}{\left[1+\left(\frac{d}{dz} p_\alpha(z)\right)^2\right]^{\frac{3}{2}}}$$

The resulting curvatures were averaged across all rotation angles resulting in one curvature value κ per filling state. A negative curvature indicates that the IVS is in its neutral position ($\kappa < 0$), while a positive curvature indicates a shift of the IVS toward the LV ($\kappa > 0$).

Volume states. We assessed the curvature of the IVS using distinct biventricular volume states per heart phantom. Based on prior data demonstrating effects of LVAD pump speeds on LV and RV volumes,[7] excessive LVAD support was simulated by removing volume from the LV and adding volume to the RV. Up to 40 ml were removed from the LV volume in steps of 10 ml. For each LV volume state, we added volume to the RV in steps of 10 ml from 0 ml up to 50 ml, until a clear shift of the IVS was noticed. Therefore, the experimental set-up allowed us to examine volume differences (Δ volume, LV volume – RV volume) of up to –90 ml between the LV and RV. The procedure resulted in 22, 21, 30, and 30 distinct biventricular volume states for the heart phantoms with LVEDD 6.1, 6.3, 8.1, and 8.3 cm, respectively (Figure 1B). We aggregated measurements for all biventricular volume states with equivalent Δ volume; and we report one curvature of the IVS as median (95% CI) for each Δ volume state.

Results

Clinical Perspective

Baseline characteristics. Baseline characteristics for males (n = 12,273) *versus* females (n = 3,225) in the entire cohort are described in Table 1. Females were younger, had a smaller BSA, and were more likely than males to have nonischemic HF. Females were more likely to be in cardiogenic shock

Table 1. Baseline Characteristics for Male *versus* Female Continuous-flow LVAD Recipients in the IMACS Cohort (Implant Years: January 2013–September 2017, n = 15,498)

	Male (n = 12,273)	Female (n = 3,225)	*p*
Age at implant, years	56.60 (12.90)	53.50 (13.80)	<0.001
Body surface area, m^2	2.09 (0.30)	1.87 (0.30)	<0.001
BMI, kg/m^2	27.90 (6.56)	28.10 (7.53)	0.27
Centrifugal pump	4,306 (35.1%)	1,255 (38.9%)	<0.001
Device strategy			0.10
• Bridge to transplant	6,671 (54.4%)	1,781 (55.2%)	
• Destination therapy	5,463 (44.6%)	1,399 (43.4%)	
• Bridge to recovery	127 (1.0%)	44 (1.4%)	
Ischemic heart failure etiology	4,975 (44.6%)	721 (24.0%)	<0.001
Cardiogenic shock at implant (INTERMACS 1 and 2)	1,846 (15.1%)	530 (16.5%)	<0.001
Serum sodium, meq/l	135.00 (5.02)	136.00 (4.72)	<0.001
BUN, mg/dl	32.50 (23.40)	27.4 (23.00)	<0.001
Total bilirubin, mg/dl	1.43 (1.87)	1.21 (1.67)	<0.001
CKD stage			<0.001
• CKD stage 1–2	6,343 (52.7%)	1,465 (46.0%)	
• CKD stage 3A	2,850 (23.7%)	740 (23.2%)	
• CKD stage 3B	2,128 (17.7%)	669 (21.0%)	
• CKD stage 4–5	724 (6.0%)	309 (9.7%)	
Albumin, gm/dl	3.44 (0.69)	3.42 (0.69)	0.12
AST, U/l	69.10 (289.00)	71.80 (317.00)	0.67
ALT, U/l	70.60 (258.00)	68.70 (260.00)	0.72
WBC, $\times 10^3/\mu l$	13.20 (192.00)	12.30 (209.00)	0.83
Hemoglobin, gm/dl	11.60 (4.40)	10.8 (3.65)	<0.001
INR	1.35 (0.46)	1.31 (0.46)	<0.001
RA pressure, mm Hg	12.8 (8.12)	12.8 (8.50)	0.69
PA diastolic pressure, mm Hg	25.3 (9.20)	24.2 (8.61)	<0.001
Cardiac index, $l/min/m^2$	2.05 (0.665)	2.01 (0.690)	0.02

ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; BUN, blood urea nitrogen; CKD stage, chronic kidney disease stage; INR, international normalized ratio; INTERMACS Profile, Interagency Registry for Mechanical Circulatory Support Profile; PA diastolic pressure, pulmonary artery diastolic pressure; RA pressure, right atrial pressure; WBC, white blood cell count.

(INTERMACS profiles 1–2) at implant, with lower preoperative CI. Females were more likely to have a centrifugal *versus* axial flow LVAD implanted. They were more likely to have more advanced stages of chronic kidney disease but had lower blood urea nitrogen at baseline. Additionally, they had a lower hemoglobin, and less evidence of hepatic dysfunction (lower bilirubin and international normalized ratio, higher serum sodium).

Association of female sex and LVEDD with outcomes. There were 1,466 deaths (9.5%) within 3 months postimplant, and 2,550 patients (16.5%) who had postoperative RVF. Female sex was associated with 42% increased odds of 3 month postoperative mortality (adjusted odds ratio [OR] female *versus* male 1.42, 95% CI: 1.23–1.65, $p < 0.001$), and 18% increased odds of RVF (adjusted OR: 1.18, 95% CI: 1.05–1.33, $p = 0.005$) post-LVAD.

Females had a significantly smaller preoperative LVEDD compared to males (6.49 ± 1.08 *vs.* 6.93 ± 1.32 cm, $p < 0.001$). Smaller preoperative LVEDD was independently predictive of 3 month postoperative mortality (adjusted OR per cm decrease in LVEDD: 1.20, 95% CI: 1.14–1.28, $p < 0.001$) and postoperative RVF (adjusted OR per cm decrease in LVEDD: 1.09, 95% CI: 1.04–1.14, $p < 0.001$). The addition of preoperative LVEDD to the regression models examining the influence of sex on post-LVAD outcomes attenuated the effect size of female sex on 3 month mortality post-LVAD by 14% and postoperative RVF by 13% (Table 2), indicating that smaller LVEDD partially mediated the association of female sex with these outcomes.

A sensitivity subgroup analysis by BSA demonstrated that female sex was associated with 3 month mortality in both BSA subgroups (< and ≥2.03 m^2), but female sex was associated with RVF only in smaller patients (BSA < 2.03 m^2). Smaller LVEDD attenuated the effect of sex on these outcomes (Table 3).

Experimental Perspective

Heart phantoms. The four patients used to derive the heart phantoms were 62 ± 6 years old, with a BSA of 2.1 ± 0.2 m^2 and an ejection fraction of 22.5 ± 2.5%. The smaller heart phantoms (LVEDD 6.1 and 6.3 cm) had a slightly lower baseline sphericity index (0.58 *vs.* 0.62) compared with the larger hearts (LVEDD 8.1 and 8.3 cm) (Figure 1B), indicating more spherical preoperative remodeling in the larger hearts.

Septum curvatures of heart phantoms. At zero Δ volume, the larger hearts demonstrated a more negative curvature (–16 [–15, –18] *vs.* –5 [–3, –7]) compared with the smaller hearts (Figure 2A).

Leftward shifted septum. The IVSs of the smaller hearts (dark grey) abnormally shifted to the left at smaller Δ volume (40 [30, 52] *vs.* 50 [48, 69] ml) compared with the IVSs of the larger hearts (light grey) (Figure 2). Once the septum had shifted, all hearts experienced similar curvatures.

Discussion

In this translational study, we combine clinical data from a large contemporary multinational registry of CF LVAD implants, with experimental data utilizing ultrasound measurements of the IVS positioning from patient-derived silicone heart phantoms to demonstrate that: (1) Smaller LV size mediates 13–14% of the increased risk of early 3 month mortality and postoperative RVF in female LVAD recipients, and (2) the IVS of smaller hearts shifts abnormally to the left at smaller Δ volumes compared with that of larger hearts. Prior data have demonstrated that adverse hemodynamic consequences during CF LVAD support may result from leftward IVS shifting.[4–6,8–12] Building on this hypothesis, we suggest that LV size-LVAD mismatch of smaller LVs mediates in part, the worse post-LVAD outcomes for female patients, due to lower Δ volume thresholds for leftward shift of the IVS in smaller hearts.

Several prior studies have demonstrated worse mortality and postoperative RVF for females after LVAD compared with males. Contemporary data from Intermacs[1] and IMACS[3] have identified female sex as a risk factor for increased early (3–4 months) mortality after LVAD implant. While these analyses did not include patients with the HeartMate 3™ LVAD,[21] DeFillipis and colleagues recently studied bridge to transplant patients from the United Network for Organ Sharing database including 365 HeartMate 3™ patients and found that female sex was associated with higher waitlist mortality independent of device type.[17] An analysis of EUROMACS that included 966 patients implanted between 2011 and 2014 found that females

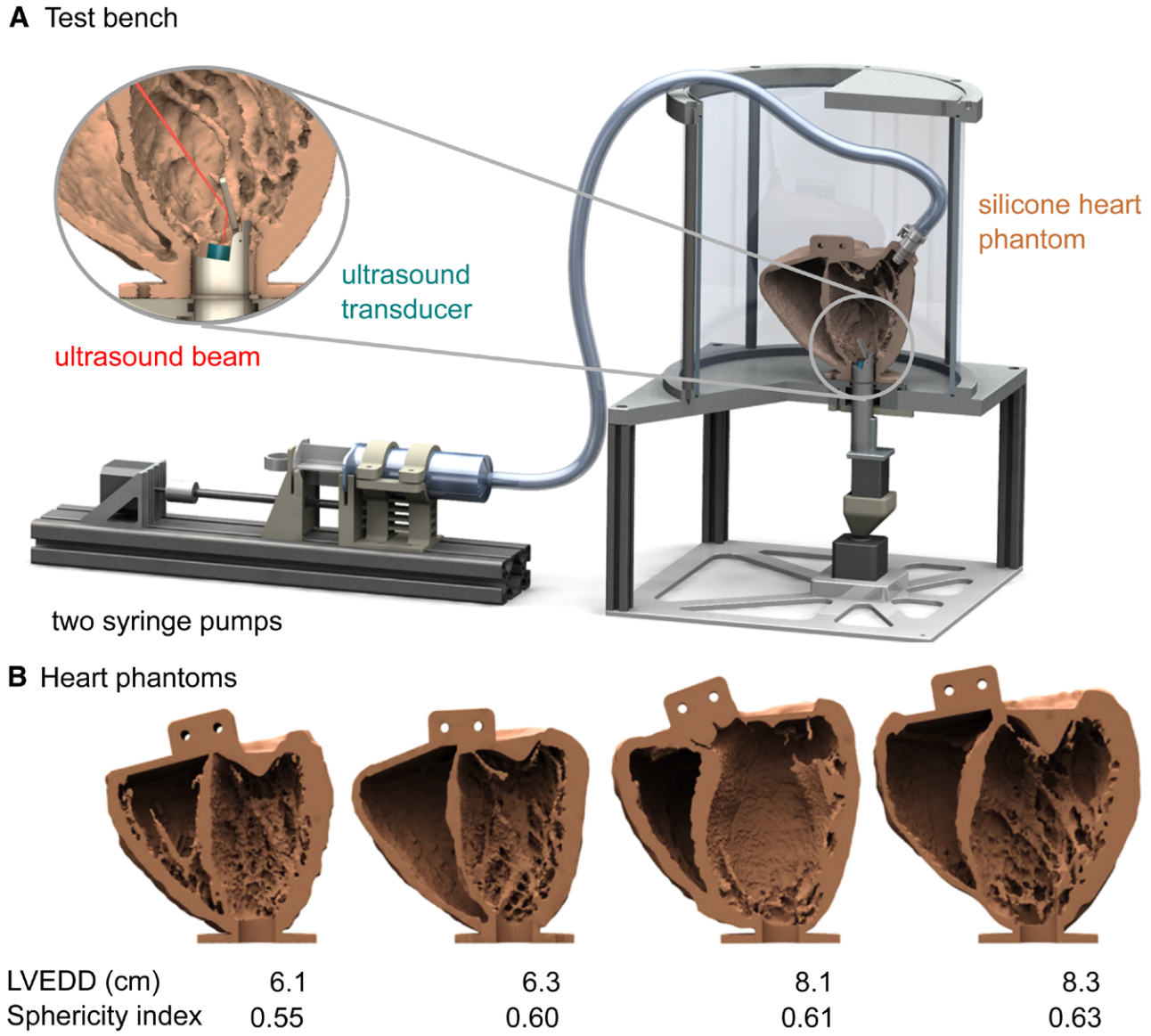

Figure 1. Test bench featuring (A) a steerable ultrasound beam integrated in a placeholder left-ventricular assist device cannula and (B) four distinctly sized silicone heart phantoms.

are at higher risk of RVF requiring additional RV support after implant[22]; confirming prior observations in smaller cohorts by Birks *et al.*[23] and Weymann *et al.*[24] While we have recently demonstrated that smaller LV size mediates a portion of the increased risk of early 3 month mortality in females, there remains a paucity of data on the underlying mechanisms for these disparities in outcomes.[3] In the current study, we demonstrate for the first time that smaller LV size also mediates ~13% of the increased risk specifically of RVF in females.

Few studies have demonstrated an association between smaller LV size and worse outcomes after LVAD implant, although none have studied the underlying hemodynamic mechanisms for this observation. Shah *et al.* studied 9,424 LVAD recipients implanted between 2008 and 2015 from the Intermacs registry to find an 11% increased hazard of postimplant death for each centimeter decrease in LVEDD.[25] Similarly, in a smaller study of 83 LVAD patients, Topilsky *et al.* demonstrated that a smaller LVEDD (<6.3 cm) was associated with higher risk for 30 day death or RVF after implant.[26] They found that the risk of adverse events almost tripled when the preimplant LVEDD was below 6.3 cm.[26] Building upon the findings of these studies, we utilized experimental phantom heart modeling to show that smaller hearts (LVEDD <6.3 cm) are prone to leftward IVS shifts at smaller Δ volume thresholds. Leftward IVS shift in turn mediates RVF and mortality by increasing RV wall stress (*via* La-Place's law), reducing RV contractility, worsening tricuspid regurgitation, and increasing ventricular suction events.[4–6,8–12]

Septal curvature has been studied primarily using cardiovascular imaging,[7,27] and recently using computational engineering methods.[28] An extensive echocardiographic LVAD ramp study observed volume decreases in the LV of 127 ml and 51 ml, and volume increases in the RV of 60 ml and 22 ml across the operating range of the HeartMate II and the HVAD, respectively.[7] Although these volume changes were more severe than in our study (maximum of 50 ml), the authors noted

Table 2. Association of Female Sex and Left-Ventricular End Diastolic Diameter with postoperative mortality and RVF in the IMACS Registry

	Model 1		Model 2		
	Adjusted OR [95% CI]	*p*	Adjusted OR [95% CI]	*p*	Attenuation of β-estimate
Postoperative RVF					
Female sex	1.18 [1.05–1.33]	0.005	1.16 [1.03–1.30]	0.02	13.25%
LVEDD (per cm decrease)	1.09 [1.04–1.14]	<0.001	1.08 [1.03–1.12]	0.001	
3 month mortality					
Female sex	1.42 [1.23–1.65]	<0.001	1.36 [1.17–1.57]	<0.001	14.12%
LVEDD (per cm decrease)	1.20 [1.14–1.28]	<0.001	1.19 [1.12–1.27]	<0.001	

Model 1: Adjusted for age, BSA, pump type, HF etiology, cardiogenic shock at implant (INTERMACS profiles 1-2), eGFR, serum sodium, BUN, total bilirubin, hemoglobin, INR, PA diastolic pressure, cardiac index.

Model 2: Adjusted for all covariates in Model 1 + sex + LVEDD.

BSA, body surface area; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate (by Modification of Diet in Renal Disease (MDRD) equation); HF, heart failure; INR, international normalized ratio; INTERMACS Profile, Interagency Registry for Mechanical Circulatory Support Profile; LVEDD, Left-ventricular end-diastolic diameter; OR, odds ratio; PA, pulmonary artery; RVF, right-ventricular failure.

that not all patients showed increases in septal curvature from the lowest to highest speed setting.[7] The authors did not provide correlations between septal curvature and initial LV cavity size. Based on our experimental results, we suggest that pump speed changes can lead to critical Δ volumes, resulting in a leftward shifted septum in small hearts. Furthermore, we noted that the initial septal curvatures of the larger hearts were more negative (less shifted toward the LV), a finding we hypothesize may be in part related to the more spherical geometry of highly dilated hearts. These findings suggest that hearts with a larger LVEDD may be more resistant to IVS shifting than the smaller hearts, reducing the tendency for leftward septal shift, even with excessive LVAD support.

The findings of our study are particularly important as they suggest several clinical and engineering approaches to address the excess mortality and morbidity in females after LVAD implant. Outcomes in females may be improved by earlier and more frequent ramp study hemodynamic and echocardiography guided pump speed adjustments in the first 3 months after implant, indexing LVAD pump speeds for BSA,[29,30] as well as avoidance of excessive LV offloading mediated by over-diuresis or excessive LVAD pump speed. During ramp studies, septal curvature is measurable using three-dimensional echo and may serve as valuable at assessing the LV-RV interaction. Algorithms for augmented three-dimensional echo to assess local RV curvatures have been previously proposed.[7] Similar approaches target vertical septal curvature for pump speed adaptation.[31] Moreover, we envision device innovations where sensor technology is integrated in the LVAD cannula.[13,14] Breakthroughs in capacitive micromachined ultrasound transducers enable the integration and miniaturization of ultrasound technology.[32,33] Integrated ultrasonic transducers could monitor the IVS position in real time for automatic pump speed adaptation. Our study utilized an ultrasound transducer equivalent to a probe with 156 individual transducers and would generate a large amount of data if used in real time. However, in a recent study, we were able to demonstrate 80% accuracy in predicting the septum position with only three transducers.[13]

Table 3. Association of Female Sex and Left-Ventricular End Diastolic Diameter With Postoperative Mortality and RVF in the IMACS Registry, Stratified by Median BSA (2.03 m²)

	Model 1		Model 2		
	Adjusted OR [95% CI]	*p*	Adjusted OR [95% CI]	*P*	Attenuation of B-estimate
BSA lower than median (2.03 m²)					
Postoperative RVF					
Female sex (n = 2,305)	1.26 [1.09–1.45]	0.001	1.22 [1.06–1.40]	0.007	14.41%
LVEDD (per cm decrease)	1.11 [1.05–1.19]	0.001	1.10 [1.03–1.18]	0.003	
3 month mortality					
Female sex (n = 2,305)	1.34 [1.12–1.60]	0.001	1.26 [1.06–1.51]	0.01	20.82%
LVEDD (per cm decrease)	1.24 [1.14–1.33]	<0.001	1.20 [1.12–1.32]	<0.001	
BSA higher than median (2.03 m²)					
Postoperative RVF					
Female sex (n = 920)	0.93 [0.77–1.13]	0.47	0.92 [0.75–1.12]	0.38	NA
LVEDD (per cm decrease)	1.04 [0.89–1.11]	0.17	1.04 [0.98–1.11]	0.15	
3 month mortality					
Female sex (n = 920)	1.36 [1.06–1.77]	<0.001	1.30 [1.00–1.68]	0.05	16.08%
LVEDD (per cm decrease)	1.16 [1.08–1.27]	<0.001	1.16 [1.06–1.27]	0.001	

Model 1: adjusted for age, pump type, HF etiology, cardiogenic shock at implant (INTERMACS profiles 1-2), eGFR, serum sodium, BUN, total bilirubin, hemoglobin, INR, PA diastolic pressure, cardiac index.

Model 2: Adjusted for all covariates in Model 1 + sex + LVEDD.

BSA, body surface area; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate (by Modification of Diet in Renal Disease (MDRD) equation); HF, heart failure; INR, international normalized ratio; INTERMACS Profile, Interagency Registry for Mechanical Circulatory Support Profile; LVEDD, left-ventricular end-diastolic diameter; OR, odds ratio; PA, pulmonary artery; RVF, right-ventricular failure.

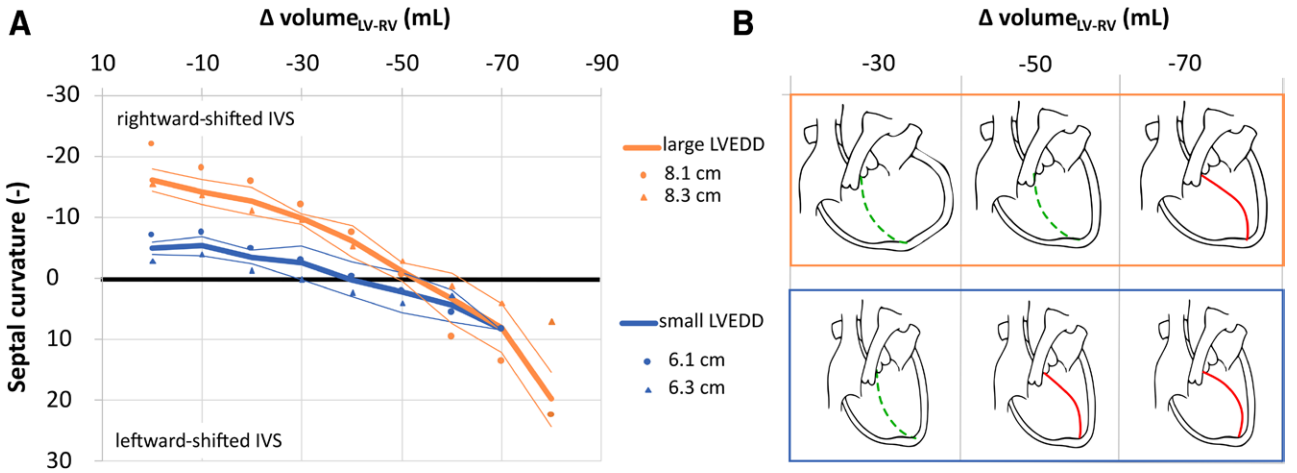

Figure 2. Curvature depicted as median (solid line) with 95% CI (dashed line) observed in two small and two large biventricular heart phantoms upon administration of a volume change between the LV and the RV (Δ volume). The zero crossing of the curvature indicates a septum shift. The septum of the smaller hearts (dark grey) shifts at a smaller Δ volume compared to the larger hearts (light grey). IVS, intraventricular septum; LVEDD, left-ventricular end-diastolic diameter; LVV, left-ventricular volume; RVV, right-ventricular volume.

Limitations

Although we utilized a multinational "real-world" registry cohort to study the association of sex and LVEDD with outcomes, participation in the IMACS database is voluntary, and whether the data are truly generalizable is unknown. In addition, echocardiographic determination of LVEDD is subject to interobserver variability. Other variables that might influence outcomes, such as country, implant center, and race/ethnicity, are not available in the IMACS registry. Since the IMACS registry does not include HeartMate 3™ LVAD recipients, the observed associations of LV size with outcomes require validation in HeartMate 3™ LVAD recipients. Furthermore, the conclusions derived from the experimental data are limited to a static observation of the end-diastolic cardiac phase. Hence, there is a clear need to prove validity of the *in vitro* observations in the clinical setting.

Conclusions

In this proof-of-concept translational research study, we demonstrate that smaller heart size and resultant LV size-LVAD mismatch partially mediates worse post-LVAD outcomes for female patients due to lower Δ volume thresholds for leftward shift of the IVS in the smaller female hearts. Future studies are underway to examine the impact of variable RV loading, apical pericardial pump fixation, and pump suction on IVS function during LVAD support. Positive findings are expected to be highly relevant to: first, explaining the findings of the large clinical cohort assessed in this study and second, LVAD speed setting post implantation. A similar bedside-to-bench approach is necessary to understand and bridge sex disparities in heart failure outcomes.

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