Circulation: Heart Failure

ORIGINAL ARTICLE

Impact of Baseline Hemodynamics on the Effects of a Transcatheter Interatrial Shunt Device in Heart Failure With Preserved Ejection Fraction

BACKGROUND: Interatrial shunt device (IASD) effects have been described in patients with heart failure and ejection fractions (EFs) ≥40%. However, baseline characteristics that correlate with greatest hemodynamic effects are unknown. On the basis of fundamental principles, we hypothesized that larger pressure gradients between left and right atria would yield greater shunt flow and greater hemodynamic effects.

METHODS AND RESULTS: REDUCE LAP-HF (Reduce Elevated Left Atrial Pressure in Patients With Heart Failure) was a multicenter study that investigated IASD safety and performance. Sixty-four patients with EF ≥40% underwent device implantation followed by hemodynamic assessments at rest and exercise, including pulmonary capillary wedge pressure (PCWP, surrogate for left atrial pressure) and central venous pressure (CVP). At 6 months, IASD resulted in an average pulmonary-to-systemic blood flow ratio of 1.27 and increased exercise tolerance. The PCWP-CVP gradient (ie, the driving pressure for shunt flow) decreased at peak exercise from 16.8±6.9 to 11.4±5.5 mm Hg, because of increased CVP (17.5±5.4 to 20.3±7.9 mm Hg; P=0.04) and decreased PCWP (34.1±7.6 to 31.6±8.0 mm Hg; P=0.025). Baseline PCWP-CVP gradient during exercise correlated with changes of both PCWP-CVP and PCWP: $\Delta(\text{PCWP-CVP})=10.0-0.89\cdot(\text{PCWP-CVP})_{\text{baseline}}$ (r^2=0.56) and $\Delta\text{PCWP}=7.54-0.60\cdot(\text{PCWP-CVP})_{\text{baseline}}$ (P=0.001). Hemodynamics of patients with EF ≥50% and those with EF <50% responded similarly to IASD.

CONCLUSIONS: In heart failure patients with EF ≥40%, IASD significantly reduced PCWP and PCWP-CVP at peak exercise. Patients with higher baseline PCWP-CVP gradient had greater reductions in both parameters at follow-up. Results were sustained through 12 months and were independent of whether EF was ≥50% or between 40% and 49%. Additional studies will help further define the baseline hemodynamic predictors of exercise, hemodynamic, and clinical efficacy of the IASD.

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WHAT IS NEW?

- Interatrial shunt devices have been shown to reduce work-normalized pulmonary capillary wedge pressure (PCWP) during exercise and are being further investigated as a therapy for patients with heart failure and preserved ejection fraction. However, baseline factors that correlate with greatest reductions of PCWP are not known.
- We show that the greater the difference between PCWP and central venous pressure (which is the driving force for flow through the shunt), the greater is the reduction on this pressure gradient and the greater the reduction of PCWP at peak exercise.

WHAT ARE THE CLINICAL IMPLICATIONS?

- Interatrial shunt devices have already received Conformité Européene marking in the European Union and are being investigated in the United States. The current results may help guide clinicians on how to evaluate and identify patients who are most likely to benefit, at least in terms of reductions of PCWP.
- Additional work is ongoing to determine whether reductions of PCWP correlate with clinical outcomes.

Heart failure (HF) with preserved ejection fraction (HFpEF) accounts for more than half of all cases of HF with a prevalence that continues to increase.[1] This rising burden has been accompanied by disappointing therapeutic results as effective treatment options remain elusive.[2] As the exploration of alternative management options continues, increasing emphasis has been placed on the multitude of HFpEF phenotypes and the wide range of mechanisms that contribute to the common spectrum of signs and symptoms.[3]

However, regardless of cause, HFpEF patients all demonstrate excessive increases in left atrial (LA) pressures in particular during exercise which contributes to effort intolerance and portends a worse prognosis.[4–8] The understanding of the mechanisms underlying such hemodynamic changes has evolved from the now outdated singular concept of diastolic dysfunction to include abnormalities in blood volume regulation, increased pericardial restraint and increased sensitivity of blood volume distribution to acute neurohormonal stimulation during exercise[3,9–14] and volume loading.[6,15,16] Although many gaps in understanding remain, these studies have led to the concept that exercise-induced increase of LA pressure is a viable therapeutic target for these patients.[17–21]

We recently introduced a device-based therapeutic strategy that establishes an interatrial communication to allow left-to-right shunting and reduce LA pressure.[17,22–27] Fundamentally, an interatrial shunt will reduce the pressure gradient between the LA and right atria (RA). In the setting of HF, where LA pressure (for which pulmonary capillary wedge pressure [PCWP] serves as a surrogate) is elevated above RA pressure (and its equivalent, central venous pressure [CVP]), a left-to-right shunt is expected and has been demonstrated in our initial clinical studies with the interatrial shunt device (IASD) including a randomized controlled trial.[23,24,27] However, the baseline characteristics that are associated with better hemodynamic and clinical outcomes have not been investigated. Basic principles and theories of shunt hemodynamics[17] suggest that at a given diameter, shunt flow and the ability to reduce LA pressure is driven by the preexisting pressure gradient between atria, which is indexed by the difference between PCWP and CVP. Accordingly, the purpose of the present study was to better define changes in PCWP, CVP, and their difference in response to exercise and test whether the PCWP-CVP gradient correlates with hemodynamic response to IASD.

METHODS

The data and study materials from this study will not be made available to other researchers.

Study Design and Subjects

The REDUCE LAP-HF study (Reduce Elevated Left Atrial Pressure in Patients With Heart Failure) was a multicenter, prospective, open-label, single-arm study designed to investigate the safety and performance of a transcatheter, transvenous IASD (IASD system II; Corvia Medical Inc, Tewksbury, MA). The study design has been previously described in detail.[22]

Patients with HF and EF ≥40% (assessed by the clinical site) were eligible for study inclusion if they were adults (aged >40 years) with evidence of chronic symptomatic HF (New York Heart Association functional classes II–IV) and increased PCWP (>15 mm Hg at rest, or >25 mm Hg during supine bicycle exercise) measured during right heart catheterization. Patients were excluded for substantial right ventricular dysfunction indexed by elevated CVP (>14 mm Hg) or tricuspid annular plane systolic excursion <14 mm, as well as for recent (<3 months) myocardial infarction, coronary artery bypass graft, or percutaneous coronary intervention; nonambulatory New York Heart Association IV HF, infiltrative or obstructive hypertrophic cardiomyopathy, moderate or greater aortic stenosis or mitral regurgitation, and severe renal dysfunction. The study protocol was approved by the ethics and institutional review committees at each institution and country-specific competent authorities, and all patients gave informed consent.

The EF inclusion criterion for HFpEF was consistent with prior studies (see for example[28]). However, subsequent to the start of the present study, new guidelines were published that

defined HFpEF as EF ≥50% and HF with midrange EF (HFmrEF) as EF 40% to 49%. As detailed below, the impact of EF range on the results was examined.

Procedures

All patients underwent right heart catheterization with assessment of cardiac output and central hemodynamics (RA pressure, pulmonary artery pressure [PAP], and PCWP) at rest and during supine bicycle exercise at the following time points: baseline, 6 months, and optionally at 12 months after device implantation. Right heart catheterization was performed from either an antecubital or internal jugular vein with a 7F or 8F sheath. Cardiac output was determined by thermodilution (at rest and during exercise) made at least in triplicate and by Fick method at rest only; for the latter, oxygen consumption was assumed to be related to sex, age, and heart rate according to a previously validated equation and calculated at the hemodynamic core laboratory to ensure consistency of calculations.[29] After baseline resting hemodynamic measurements, measurements were taken 5 minutes after raising legs into the bicycle pedals and then during symptom-limited supine bicycle exercise starting at 20 W with 20 W increments every 3 minutes until the patient achieved maximum effort (defined by symptom-limiting dyspnea or fatigue). Resting blood samples were collected from the pulmonary artery and superior and inferior vena cavae at the preimplant baseline and follow-up tests to measure oxygen saturation for assessment of left-to-right shunting as indexed by the pulmonary-to-systemic blood flow ratio (Qp:Qs). For calculation of Qp:Qs, we assumed that mixed venous oxygen saturation (S_{MV}) was determined by $S_{MV}=(3\cdot S_{SVC}+S_{IVC})/4$, where S_{SVC} and S_{IVC} were blood oxygen saturations in the superior and inferior vena cavae S_{MV}, respectively. Qp:Qs was then calculated as $(S_A-S_{MV})/(S_A-S_{PA})$, where S_A is the oxygen saturation of arterial blood; and S_{PA} is oxygen saturation of pulmonary arterial blood.

Device insertion was done within 45 days of screening evaluations. Implantation was performed percutaneously via the femoral vein on a separate occasion after hemodynamic qualification. Standard trans-septal puncture of the interatrial septum was performed using the operator's preferred technique, using fluoroscopy and transesophageal or intracardiac echocardiography, and the implant was inserted and positioned using an over-the-wire technique. The IASD had an internal diameter of 8 mm.

Outcomes

The primary objective of this study was to assess exercise-induced hemodynamic changes 6 and 12 months after device implantation. The hemodynamic end points measured were Qp:Qs, cardiac output, CVP, PAPs, PCWP, pulmonary vascular resistance, and aortic pressures. Resting forward cardiac output was assessed by indirect Fick method using the estimated S_{MV} (as quantified above). Hemodynamic tracings were analyzed at an independent core laboratory (PVLoops LLC, NY).

Analyses

Hemodynamic tracings at each stage of exercise were printed, scanned, and sent to a core laboratory for independent quantification of pressures at rest and at each stage of exercise. Baseline and follow-up tests were read independently of each other to reduce bias.

Normally distributed data are presented as mean (SD) and nonparametric data as median (interquartile range). We used a paired *t* test or Wilcoxon matched pair sign-rank test as appropriate to compare follow-up data versus baseline data. Linear regression analysis was applied to data at peak exercise and compared with baseline data by ANCOVA. The null hypothesis was rejected at $P<0{\cdot}05$.

Since the primary driver of flow through an IASD is the pressure gradient between RA and LA, we examined the baseline PCWP-CVP difference and how it changed in response to the presence of the IASD. Second, to understand the determinants of changes in the PCWP-CVP gradient, we examined plots of CVP versus PCWP to better elucidate the simultaneous impact of exercise on right- and left-sided hemodynamics before and after IASD implant. As in prior studies,[30,31] we divided the PCWP-CVP diagram into 5 quadrants (or zones) at rest and during exercise corresponding with different states of left- and right-sided congestion: a normal zone with normal CVP and PCWPs; a zone of primary left-sided congestion with elevated PCWP and normal CVP; a zone of primary right-sided congestion with elevated CVP and normal PCWP; a zone with combined right- and left-sided congestion with elevated CVP and PCWP; and a state of relative hypovolemia with both CVP and PCWP below the normal lower limits (detailed further below). On the basis of recently published resting and exercise data,[8,32,33] normal upper limits for CVP and PCWP at rest were set at 10 and 15 mm Hg, respectively. Normal upper limits for CVP and PCWP during exercise were set at 16 and 26 mm Hg, respectively. Finally, to assess the IASD operating characteristics, we explored hemodynamic factors that correlated with reductions of the PCWP-CVP gradient and reductions of PCWP at rest and during exercise.

RESULTS

Sixty-four patients underwent implantation of the IASD system. The demographics have been detailed previously[23,24] and are summarized briefly in Table 1, in which demographics are also compared between patients with EF ≥50% and patients with EF <50%. There were no significant differences in clinical characteristics between these 2 subgroups (additional details below) except for the difference in EF and a greater proportion of New York Heart Association III patients in the EF <50% group (36% versus 72%).

The group-averaged resting and peak exercise hemodynamic parameters at baseline and 6 months post-IASD are summarized in Table 2. Most of these data have been described previously.[23] In brief, the key hemodynamic effects of IASD under resting conditions included a Qp:Qs (calculated from vena caval and pulmonary artery oxygen saturations) of 1.27±0.24 which resulted in increased resting cardiac output measured by thermodilution (indicative of flow through the pulmonary circulation) and no

Table 1. Patient Characteristics

Variable	All Patients (n=64)	EF≥50% (n=23)	EF<50% (n=41)	*P* Value
	Mean±SD or %	Mean±SD or %	Mean±SD or %	
Age, y	69±8	69.7±7.7	69.4±8.8	0.90
Sex (M/F)	42/22	15/8	27/14	0.75
NYHA class (II/III)	27/73	9/14	9/32	0.01
BMI, kg/m^2	33±6	32±4	33±7	0.35
Comorbidities				
Diabetes mellitus (%)	34	35	34	0.95
Hypertension (%)	81	80	81	1.00
Atrial fibrillation (%)	61	50	68	0.17
CAD (%)	23	20	24	1.00
MLWHFQ	49±20	46±18	51±20	0.32
Six-minute walk test, m	309±108	335±111	294±106	0.16
Echocardiography (Core Laboratory)				
LV end-diastolic volume index, mL/m^2	68±13	62±16	71±13	0.01
LVEF (%)	47±7	55±4	43±5	<0.001
LV mass index, g/m^2	119±36	117±39	120±35	0.81
LA volume index, mL/m^2	34±17	30±9	38±20	0.18
RV diastolic volume index, mL/m^2	22±9	21±8	23±9	0.24
RA volume index, mL/m^2	35±17	31±16	37±18	0.24
E/A ratio	1.3±0.8	1.2±0.6	1.4±0.9	0.37
E/e′ ratio	13.9±5.9	13.7±4.3	14.0±6.7	0.88
TAPSE, mm	20±4	21±3	20±5	0.37
NT-proBNP, pg/mL (median, IQR)	377 (222–925)	287 (100–460)	572 (257–1208)	0.09

BMI indicates body mass index; CAD, coronary artery disease; E/e′ ratio, the average of septal and lateral annuli motion; EF, ejection fraction; IQR, interquartile range; LA, left atrium; LV, left ventricular; M/F, male/female; MLWHFQ, Minnesota Living With Heart Failure Questionnaire; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RA, right atrium; RV, right ventricle; and TAPSE, tricuspid annular plane systolic excursion.

change in resting cardiac output assessed by indirect Fick method (indicative of flow to the systemic circulation). There was a small increase in resting CVP and a small decrease in resting PCWP. In the majority of patients, the PCWP-CVP pressure difference decreased from baseline to 6 months after the IASD implant (Figure 1A; note that in this and subsequent figures, the red symbols represent data from patients with EF ≥50%, whereas black symbols represent patients with EF <50%). However, there was noticeable variability and the pressure gradient increased in some patients.

Peak exercise tolerance increased 6 months after IASD from 42.5±18.3 W at baseline to 49.0±20.3 W at 6 months (*P*=0.002). Work- and weight-normalized PCWP (PCWP/(W/kg)) decreased significantly from 89.1±53.5 at baseline to 70.5±42.8 at 6 months post-IASD (*P*<0.001). As was the case at rest, the CVP at peak exercise increased, whereas PCWP decreased. Also, as was the case at rest, the PCWP-CVP pressure difference at peak exercise decreased 6 months after IASD implant, and there was significant variability (Figure 1B).

CVP-PCWP Relationships at Rest and Exercise

A further understanding of the impact of the IASD was revealed on examining the relationship between CVP and PCWP in individual patients as illustrated in Figure 2A and as summarized in Table 3. At baseline in the resting state, 37% of patients fell in the normal zone with PCWP and CVP within normal limits. Twenty-seven percent of patients were in the zone with ↑PCWP and normal CVP, and 34% in the ↑PCWP/↑CVP zone. Six months after IASD, resting CVP and PCWP were more closely correlated to each other than at baseline (Figure 2B); the percentage of patients in the normal zone was similar to baseline, but there was a lower percentage of patients in the ↑PCWP quadrant and an increased percentage in the ↑PCWP/↑CVP quadrant (Figure 2B; Table 3).

Table 2. Average (±SD) Resting and Exercise Hemodynamic Results From the 64 Patients Who Underwent Evaluation at Baseline and 6 Months

	At Rest			Peak Exercise		
	Baseline	6 mo	*P* Value vs Respective Baseline Values	Baseline	6 mo	*P* Value vs Respective Baseline Values
Qp:Qs	1.06±0.32	1.27±0.24	<0.001	na	na	
Peak Watts	na	na		42.5±18.3	49.0±20.3	0.002
PA O_2sat (%)	68.9±6.0	75.0±4.5	<0.001	46.9±14.8	55.7±12.5	<0.001
HR, beats per minute	68±14	70±12		95±18	100±20	0.019
CO, TD, L/min	5.5±1.6	6.7±1.5	<0.001	8.7±2.6	10.2±2.7	<0.001
CO, Fick, L/min	4.6±1.2	4.8±1.3		na	na	
CVP, mm Hg	9.0±3.7	10.6±5.1	0.027	17.5±5.4	20.3±7.9	0.041
PAS, mm Hg	37±11	38±10		66±14	67±14	
PAD, mm Hg	17±5	17±5		33±8	32±8	
PAM, mm Hg	24±7	24±6		43±9	43±9	
PCWP, mm Hg	17.4±5.2	16.5±6.7		34.1±7.6	31.6±8.0	0.025
PCWP-CVP, mm Hg	8.3±4.1	6.1±2.7	<0.001	16.8±6.9	11.4±5.5	<0.001
PVR, mm Hg L^{-1} min^{-1}	1.3±0.7	1.2±0.5		1.2±0.7	1.1±0.6	
AoS, mm Hg	143±23	143±21		170±28	180±30	0.005
AoD, mm Hg	72±13	74±10		88±19	95±23	0.02
AoM, mm Hg	96±14	97±12		114±20	122±21	0.003
PCWP/(W/kg)	na	na		89.1±53.5	70.5±42.8	<0.001

Values without *P* values are not significantly different. AoD indicates aortic diastolic; AoM, aortic mean pressures; AoS, aortic systolic; CO, cardiac output; CVP, central venous pressure; HR, heart rate; na, not available; PA, pulmonary artery; PAD, pulmonary artery diastolic; PAM, pulmonary artery mean pressures; PAS, pulmonary artery systolic; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; Qp:Qs, the ratio of flows through the pulmonary and systemic circulations; and TD, thermodilution.

During exercise at baseline, and accounting for exercise-appropriate normal upper limits, 8% of patients fell in the normal hemodynamic quadrant, 33% were in the ↑PCWP quadrant, and 59% were in the combined ↑PCWP/↑CVP quadrant (Figure 2C; Table 3). At 6 months after IASD implant, there was a greater percentage of patients in the normal quadrant, fewer in the ↑PCWP quadrant and similar numbers in the ↑CVP and ↑PCWP/↑CVP quadrants (Figure 2D; Table 3). Linear regression analysis applied to the data at peak exercise showed that the PCWP-CVP relationship was shifted downward by ≈4.7 mm Hg at 6 months compared with baseline by ANCOVA which yielded the following regression coefficients: PCWP=20.9 (1.7)–4.7 (1.1)·Treatment+0.76 (0.08)·CVP (values in parentheses are SE of respective coefficients), where Treatment is a dummy variable that equals 0 for data obtained at baseline (before IASD) and 1 for data obtained at 6 months after IASD (*P*<0.0001 for all coefficients). In contrast, there was no impact of treatment on the slope of this relationship (*P*=0.65).

Exercise-induced increases in PCWP were greater than concomitant increases in CVP; this is important because it suggests that the pressure gradient driving left-to-right flow increases during exercise and that the IASD-mediated reductions in PCWP will be greater during exercise. There was a weak correlation between the increase of PCWP from rest to peak exercise (ΔPCWP) and the increase of CVP from rest to peak exercise (ΔCVP): ΔPCWP=13.7 (1.8)+0.38 (0.19)·ΔCVP (*P*=0.05, r^2=0.065). Six months after IASD, these 2 parameters became more tightly correlated, presumably because of the communication between RA and LA: ΔPCWP=11.0 (1.0)+ 0.45 (0.09)·ΔCVP.

Hemodynamic Correlations With IASD Induced Reductions in Left-to-Right Pressure Gradient

The driving force for flow through the IASD is the pressure gradient between the LA and RA which

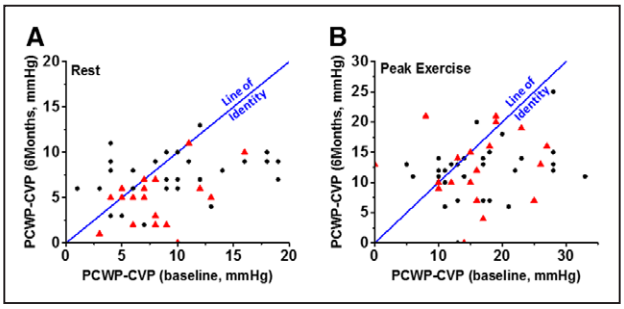

Figure 1. Difference between pulmonary capillary wedge pressure (PCWP) and central venous pressure (CVP; an index of the estimated left-to-right atrial pressure gradient) at baseline and at 6 months. Data at rest (**A**) and at peak exercise (**B**). Most data points fall below the line of identity, indicating that the gradient is reduced at 6 months compared with baseline. Data from patients with ejection fraction ≥50% shown in red; data from patients with ejection fraction <50% shown in black.

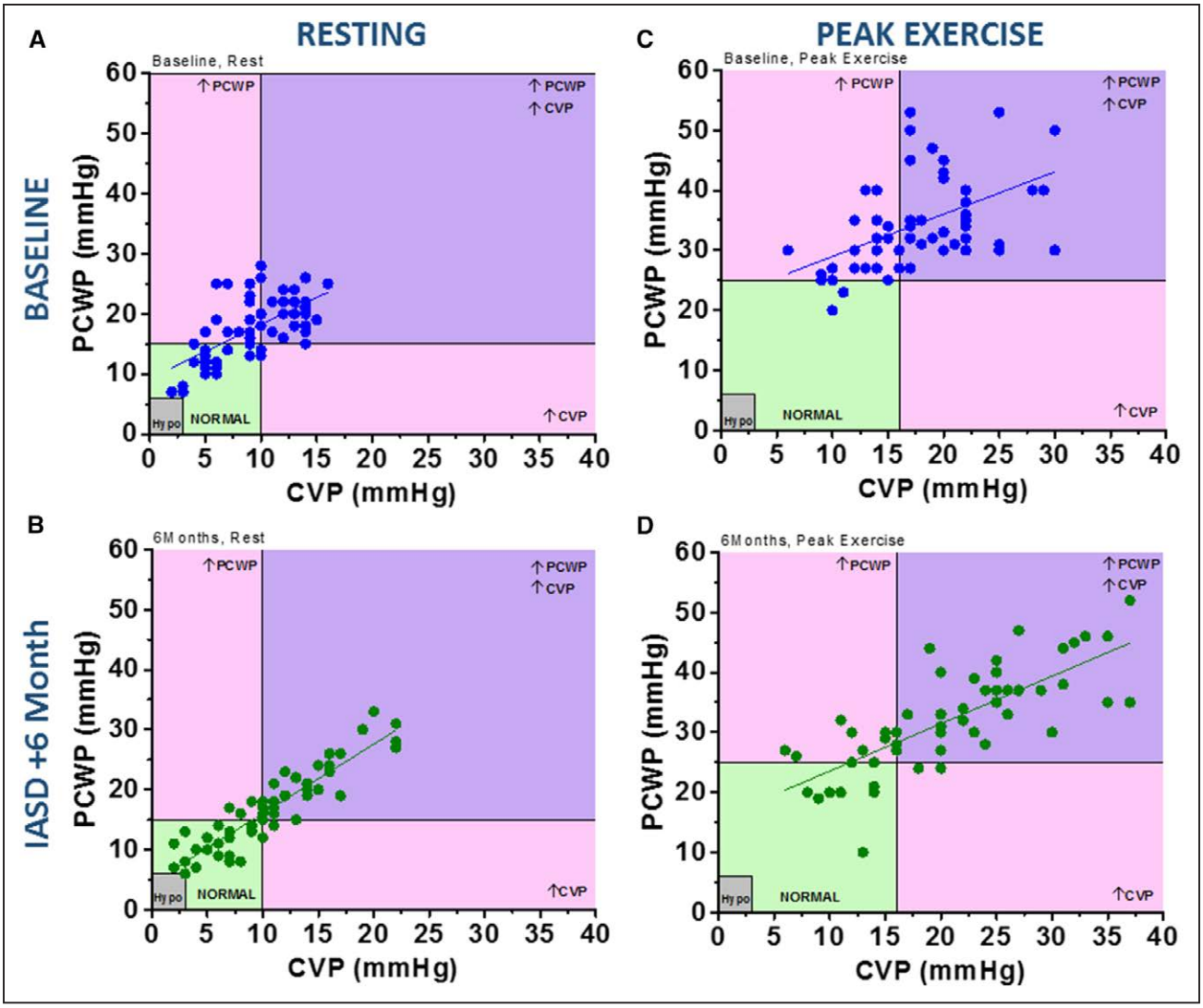

Figure 2. Relationship between central venous pressure (CVP) and pulmonary capillary wedge pressure (PCWP) in individual patients.
Data at rest shown in panels **A** and **C**; data at peak exercise shown in panels **B** and **D**. Justification of values used for upper limits of normal for CVP and PCWP, which define the normal quadrant at rest and during exercise is provided in the text. Data are shown at baseline (**A** and **B**) and 6 months after interatrial shunt device (IASD, **C** and **D**). The PCWP-CVP diagram is divided into 5 quadrants (or zones) at rest and during exercise corresponding with different states of left- and right-sided congestion: a normal zone with normal CVP and PCWPs (green); a zone of primary left-sided congestion with elevated PCWP and normal CVP (pink); a zone of primary right-sided congestion with elevated CVP and normal PCWP (pink); a zone with right- and left-sided congestion with elevated CVP and PCWP (purple); and a state of relative hypovolemia with both CVP and PCWP below the normal lower limits (gray).

is estimated by the difference between PCWP and CVP. We therefore hypothesized that a greater baseline PCWP-CVP difference should be associated with greater shunting and a greater reduction of this gradient. Notably, there were no statistically significant correlations between baseline values of hemodynamics at rest and changes in PCWP-CVP or changes in PCWP from data measured. However, at peak exercise where PCWP-CVP differences were greater, there was an inverse relationship between baseline peak exercise PCWP-CVP pressure gradient and the change of this gradient from baseline to 6 months (Δ(PCWP-CVP); Figure 3A): Δ(PCWP-CVP)=10.0 (1.9)–0.89 (0.11)·(PCWP-CVP)$_{baseline}$ (r^2=0.56, P<0.001). Δ(PCWP-CVP) at peak exercise was also inversely correlated with baseline peak exercise PCWP (Figure 3B): Δ(PCWP-CVP)=11.1 (4.4)–0.46 (0.13)·PCWP$_{baseline}$ (r^2=0.18, P<0.001). Finally, Δ(PCWP-CVP) at peak exercise was inversely correlated to Qp:Qs measured 6 months after IASD implant (Figure 3C): Δ(PCWP-CVP)=10.9 (5.3)–11.9 (4.1)·Qp:Qs (P=0.005, r^2 = 0.13). Thus, the greater the Qp:Qs, the greater the reduction of the PCWP-CVP pressure gradient.

Importantly, the reduction of peak exercise PCWP at 6 months compared with baseline (ΔPCWP) was also correlated with the baseline peak exercise PCWP-CVP pressure gradient (Figure 4): ΔPCWP=7.54 (2.5)–0.60 (0.14)·(PCWP-CVP) (P=0.001, r^2=0.23). Thus, the greater the driving pressure for shunt flow, the greater the reduction in peak exercise PCWP at 6 months.

Table 3. Percent Distribution of Patients Over the 4 Filling Pressure Quadrants at Baseline and 6 Months, at Rest, and at Peak Exercise

		Filling Pressure Quadrant*			
		Normal	Elevated PCWP	Elevated CVP	Elevated CVP and PCWP
Resting	Baseline	37	27	2	34
	6 mo	37	14	3	46
Peak exercise	Baseline	8	33	0	59
	6 mo	17	22	3	58

CVP indicates central venous pressure; and PCWP, pulmonary capillary wedge pressure.

*All numbers are percentages.

Correlations Between Hemodynamics and Exercise Tolerance

Although neither baseline hemodynamic nor clinical characteristics correlated with changes in the amount of exercise performed, there was a significant correlation between the change in PCWP and the change in work- and weight-normalized peak PCWP [ie, PCWP/(W/kg)]: Δ[PCWP/(W/kg]=–15.7 (4.7)+1.5 (0.6)·ΔPCWP (*P*=0.01).

HFpEF Versus HFmrEF

As noted above, using an EF of ≥50% to define patients with HFpEF and <50% to define HFmrEF, there were no significant differences in baseline characteristics noted in Table 1. In addition, there were no differences in most of the baseline hemodynamic parameters (including CO, pulmonary vascular resistance, and blood pressure or any resting hemodynamic parameters). However, at peak exercise, compared with the HFpEF group, CVP (18.8±5.1 versus 15.15.2, *P*=0.011) and PCWP (35.6±7.9 versus 31.3±6.3, *P*=0.029) were higher in the HFmrEF group. Nevertheless, the PCWP-CVP gradient did not differ between groups (16.9±6.8 mm Hg for HFmrEF versus 16.6±7.1 mm Hg for HFpEF, *P*=0.76). At 6-month follow-up, the PCWP-CVP difference decreased to 11.8±4.2 for HFmrEF and 11.0±6.5 for HFpEF (*P*=not significant). Regarding exercise tolerance, work- and weight-normalized PCWP values at baseline were 92.2±57.7 and 87.2±49.2 (mm Hg W^{-1} kg^{-1}) and these decreased to 73.8±44.7 and 69.0±39.0 in HFmrEF and HFpEF, respectively (*P*=not significant for differences between HFpEF and HFmrEF groups). Thus, although there were differ-

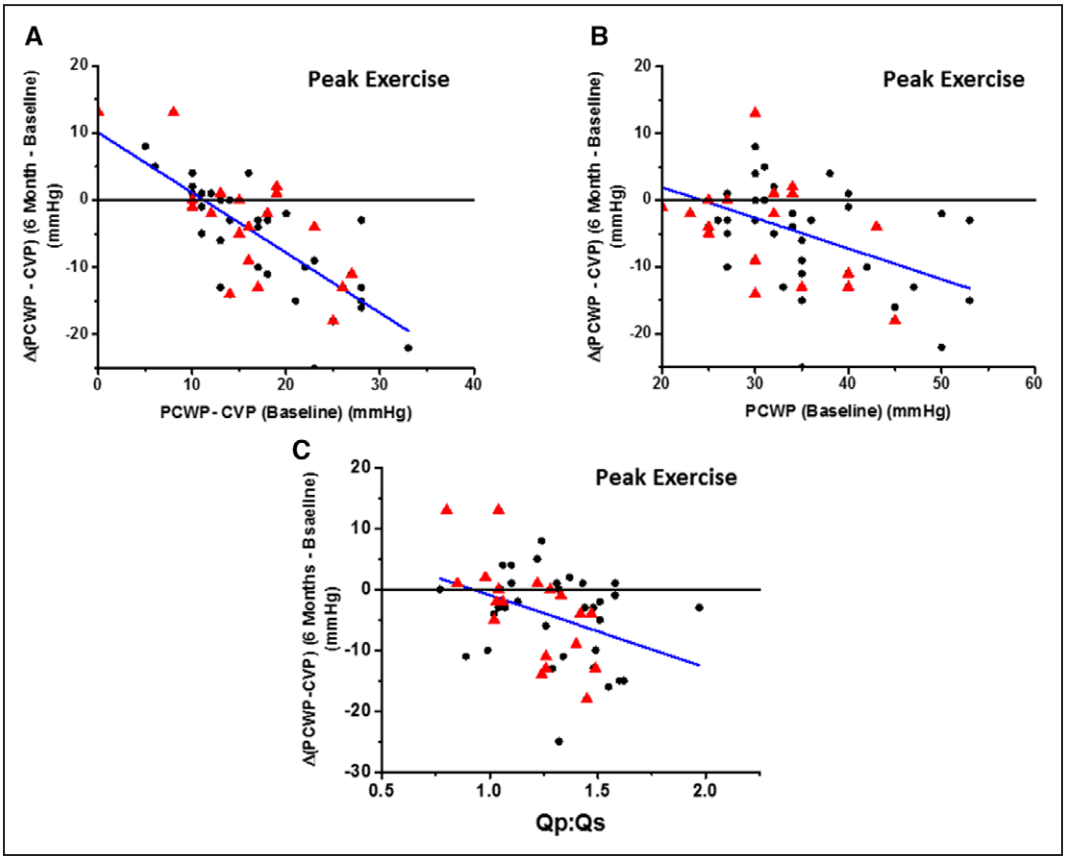

Figure 3. Baseline hemodynamic characteristics associated with InterAtrial Shunt Device (IASD)–mediated reduction in the pulmonary capillary wedge pressure (PCWP)-central venous pressure (CVP) gradient at peak exercise at 6 months.

Baseline value of PCWP-CVP (**A**), PCWP itself (**B**), and the degree of shunting as quantified by the pulmonary-to-systemic blood flow ratio (Qp:Qs; **C**) are explored. Data from patients with ejection fraction ≥50% shown in red; data from patients with ejection fraction <50% shown in black.

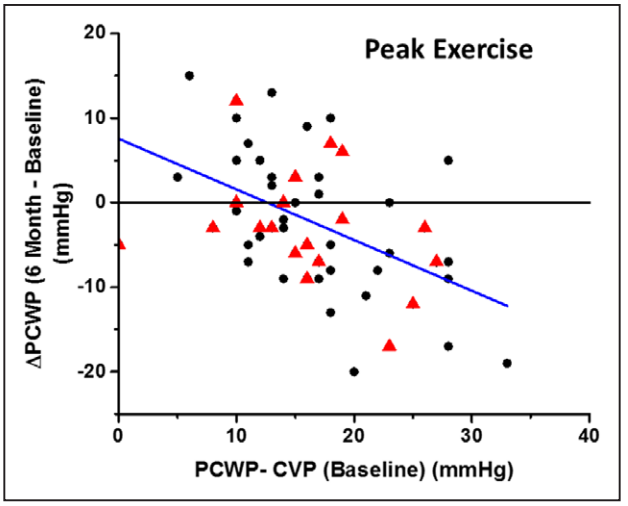

Figure 4. The interatrial shunt-mediated reduction of pulmonary capillary wedge pressure (PCWP) at peak exercise was correlated with the baseline difference between PCWP and central venous pressure (CVP).
The baseline value of the PCWP-CVP gradient is the force that drives flow through the shunt and reduces both the gradient and the value of PCWP itself. Data from patients with ejection fraction ≥50% shown in red; data from patients with ejection fraction <50% shown in black.

ences in baseline demographics and hemodynamics between patients segregated by EF, there were no differences in any of the hemodynamic and exercise responses to IASD. Similarity of responses to IASD in these 2 groups is appreciated visually in Figures 1, 3, and 4, where data from patients of the 2 groups are shown with different colored symbols.

Hemodynamics at 12-Month Follow-Up

Eighteen patients underwent a protocol-specified optional repeat exercise hemodynamic evaluation at 12 months post-IASD implantation. Results, summarized in Table 4, show that the impact on hemodynamics and exercise tolerance observed at 6 months was sustained at 12 months. However, even with the smaller number of patients, the decrease in work- and weight-normalized PCWP was statistically significant.

Effect of Changes of Diuretic Therapy

It was previously reported that the median dose of orally administered furosemide at baseline was 40 mg/d (interquartile range, 0–80).[23] Although the median dose did not change over the 6-month follow-up period so that the median change was 0 mg/d, diuretic doses were increased in 11 patients that resulted in an interquartile range from 0 to 15 mg/d. When analyzed separately, patients in whom diuretic dose either remained the same or was decreased experienced an average 4 mm Hg reduction in PCWP-CVP compared with an average 5 mm Hg reduction in the patients whose diuretic dose was increased (P=0.55). Thus, changes in diuretic dose did not impact the main findings described above.

DISCUSSION

This study examined the detailed effects of an interatrial shunt on resting and exercise hemodynamics in

Table 4. Resting and Exercise Hemodynamic Results in 18 Patients Who Underwent Protocol-Specified Evaluations at Baseline, 6 Months, and Protocol-Specified Optional Evaluation at 12 Months

	At Rest					Peak Exercise				
n=18	Baseline	6 mo	*P* Values vs Baseline	12 mo	*P* Values vs Baseline	Baseline	6 mo	*P* Values vs Baseline	12 mo	*P* Values vs Baseline
Qp:Qs	1.09±0.39	1.21±0.2		1.30±0.25						
Ex duration, min						8.2±3.4	9.7±3.18	0.03	10.4±4.24	0.05
Peak Watts						47.8±18.3	57.8±18.0	0.02	55.0±15.5	0.01
PA O_2sat (%)	69±7.4	75.0±3.6	0.003	74.4±2.78 [0.02]		44.6±15.2	51.7±11.43	0.01	56.7±17.9	0.02
CO, TD, L/min	5.2±1.2	6.3±1.4	<0.001	6.8±1.8	0.003	8.7±2.4	10.1±2.3	0.01	11.4±2.9	0.002
CO, Fick L/min	4.8±1.4	5.1±1.3		5.6±1.6	0.05					
CVP, mm Hg	8.4±3.5	10.6±5.9		10.4±3.5	0.02	17.7±6.2	20.9±8.8		21.4±8.3	0.02
PAM, mm Hg	25±8	23±7		26±8		45±11	45±11		45±13	
PCWP, mm Hg	18.8±6.1	16.4±7.5		17.4±6.0		36.3±8.5	33.4±9.1		33.2±10.4	
PCWP-CVP	10.4±4.7	5.8±2.4		7.0±3.6		19.3±7.1	12.5±4.8		11.8±6.4	
PVR, mm Hg L^{-1} min^{-1}	1.3±0.7	1.2±0.6		1.3±0.5		1.1±0.9	1.1±0.5		1.2±0.7	
AoS, mm Hg	153±21.8	147±21.06		146.6±18.89		165±36	166±37.2		178±25.9	
AoD, mm Hg	75±12	79±8		79±9.2		82±22	89±13.9		91±14.4	
AoM, mm Hg	101±13	101±10		101±10.2		110±25	114±13.2		120±12.9	
PCWP/(W/kg)						84.29±49.47	59.7±34.61	0.02	62.2±34.43	<0.001

AoD indicates aortic diastolic; AoM, aortic mean pressures; AoS, aortic systolic; CO, cardiac output; CVP, central venous pressure; PA, pulmonary artery; PAM, pulmonary artery mean pressures; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; Qp:Qs, the ratio of flows through the pulmonary and systemic circulations; and TD, thermodilution.

patients with a range of EFs spanning current definitions of HFpEF and HFmrEF. The analysis expanded the general hemodynamic results presented in prior publications.[23,24] Fundamentally, what an IASD can do is to reduce the difference between PCWP and CVP by allowing blood to flow from LA to RA; in principle, the reduced pressure gradient results from both a decrease of PCWP and an increase of CVP. Accordingly, the focus of the present study was on understanding the hemodynamic determinants of IASD-mediated reductions of PCWP-CVP gradient, CVP, and PCWP.

First, the PCWP-CVP gradient under resting conditions is relatively small. Consequently, at 6 months after IASD implantation, there was a relatively small, though statistically significant reduction of the resting PCWP-CVP gradient, an increase in CVP but no reduction of PCWP. However, resting values of CVP and PCWP were more closely correlated to each other after IASD implantation compared with baseline. Importantly, baseline resting data did not correlate with hemodynamic effects of IASD at rest noted at 6 months. At baseline (before IASD implantation) while elevations of CVP were quite significant during exercise, increases of PCWP were greater, so that the PCWP-CVP pressure difference increased dramatically during exercise. Consequently, the impact of the IASD on the PCWP-CVP gradient, PCWP, and CVP was quantitatively larger during exercise than at rest. As expected from theory,[17] the greater the PCWP-CVP difference, the greater the hemodynamic effects of IASD, on reducing both the PCWP-CVP gradient and on PCWP itself. Also consistent with theory, the greater the Qp:Qs, the greater the reduction of the PCWP-CVP difference.

The impact of IASD on PCWP at peak exercise needs to be considered within the context the change in exercise performance. Peak exercise tolerance is limited when PCWP rises with exercise beyond a threshold. The IASD does not change that threshold level. Thus, a tight correlation between changes in PCWP and changes in exercise tolerance is not expected. Instead, PCWP may approach a similar threshold at peak exercise after IASD. This was indeed the case: there were both reductions of PCWP and increases in average Watts. It is for this reason that we turn to the work- and weight-normalized PCWP (PCWP/(W/kg)) to assess the impact of IASD on exercise performance. Lower values of this parameter have been associated with improved clinical outcomes in patient with HFpEF.[7,34]

Although baseline characteristics and hemodynamics differed between patients with EF ≥50% and those with EF <50%, the impact of the IASD on hemodynamics and exercise was indistinguishable between the 2 groups, a finding what is also supported by theory (ie, that the IASD lowers PCWP by decompressing the overloaded LA, a pathophysiologic finding that is common in HFpEF and HFmrEF).

Finally, all effects noted at 6 months were sustained through the 12-month follow-up visit in the subset of patients who agreed to undergo optional repeat evaluation.

The findings noted above have implications for the inclusion and exclusion criteria for selecting patients most likely to respond, at least hemodynamically, to IASD. First, hemodynamic effects of IASD are not predicted by any parameter measured at rest; one must stress the cardiovascular system with exercise to identify hemodynamic derangements that identify favorable responders. This mirrors the diagnostic evaluation of HFpEF, where exercise assessment is necessary to identify hemodynamic perturbations that are often not apparent from assessments at steady state where cardiovascular reserve is not stressed.[4,6,8] Second, during exercise, patients with larger differences in PCWP and CVP are more likely to exhibit reductions of PCWP. Finally, EF did not influence the hemodynamic effects over the range explored.

Two other observations deserve further discussion. First, as expected and reported previously, the presence of the shunt decreased PCWP at the expense of an increase in CVP both at rest and during exercise. Because exercise is episodic, the increase of CVP during exercise may not be associated with any clinical effects. CVP did not increase further between 6 and 12 months. The consequences of a rise of CVP during rest (which was on average 1.6 mm Hg) on end-organ function (eg, renal, hepatic, etc) should be followed in long-term studies. Second, there was no impact of IASD presence on PAPs or pulmonary vascular resistance, despite the increased flow through the pulmonary arteries. This suggests that there is no detrimental effect of the increased flow on the pulmonary vasculature and its ability to dilate in the face of increased flow through 12 months of follow-up.

Several recent studies have highlighted the importance of understanding exercise hemodynamics in patients with HFpEF for guiding both the diagnosis and therapeutic developments.[2,4–6,16,19–21,35] Hemodynamics in many of these patients are relatively normal at rest (as in our study), but become rapidly abnormal on initiation of mild exercise.[4–6,13,16,20,21,35] The mechanisms underlying exercise intolerance in these patients is debated,[3,13,36] with many potential contributing factors. In addition to elevations of PCWP and limited capability to increase in stroke volume identified in many of the studies noted above, significant attention has also been placed on chronotropic incompetence.[37] However, all of these factors are inherently interrelated. Our results obtained at baseline (before IASD implant) are in excellent quantitative agreement with all prior studies in that we observed marked increases in group-averaged mean PCWP pressures, limited relative increases of peak exercise cardiac output to ≈9 L/min[8,35] (less than

reported for age-matched normal subjects[33]) and low peak heart rates.

As in our study, marked elevations of CVP have been observed during exercise in prior studies noted above but the implications have not been discussed in detail.[8] This observation may hold additional clues as to the mechanisms of disease. On an individual patient basis, exercise-induced changes in CVP were substantially greater than reported previously in age-matched normal subjects.[33] One recently proposed potential explanation for such CVP elevations is that patients with HFpEF and HFmrEF have impaired right ventricular contractile reserve (ie, inability to increase stroke volume) during exercise in addition to limited left ventricular contractile reserve.[8] However, an argument against this hypothesis is the fact that both pulmonary and systemic arterial pressures rise substantially during exercise, and more so than in normal subjects, which would not be possible if contractility of either ventricle were impaired or limited. For example, Santos et al[32] observed increases in mean PAP to 41 mm Hg in HFpEF patients (similar to our observed 45 mm Hg) in comparison to a rise to only 30 mm Hg in an age- and sex-matched control group.[33] Similar observations were made by Borlaug et al[8] who reported an increase of mean PAP to 48 mm Hg. The increase in pressure in the face of limited increases in stroke volume suggests abnormal ventricular-vascular coupling,[8] rather than impaired contractile reserve. Another potential contributing mechanism may be exercise-induced, catecholamine-mediated splanchnic venoconstriction which redistributes blood from the peripheral splanchnic to the central circulation. An older hypothesis on the role of venoconstriction in the generation of elevated PCWP and CVP in HF (regardless of EF)[38] has been recently revived, but not proven.[14] In support of such concept, a recent study demonstrated that in response to a rapidly infused bolus of saline, PCWP, mean PAP, and RA pressures increase more significantly in HFpEF patients than in controls.[15] Although it has been suggested that such changes are indicative of intrinsic ventricular diastolic dysfunction, marked changes in filling pressure because of blood volume shifts can occur in the presence of normal intrinsic diastolic properties.[39] This is relevant to the current data because increases in venous return occurring during exercise because of neurohormonal-mediated venoconstriction would be far greater than those associated with the experimental infusion of saline noted above. Finally, most recently, it has been suggested that increased pericardial constraint may also contribute to this phenomenon, an effect that seems to be more pronounced among obese HFpEF patients.[16,39] Pericardial constraints are sure to exacerbate changes in filling pressures induced by increased venous return.

Limitations

The main limitation of the present study is the lack of a parallel control group. Although the findings and conclusions of the present study are based on blinded assessment by a single core laboratory reader, non–IASD-related changes in patient hemodynamic status over the follow-up period cannot be excluded. This may include changes in compliance with diet and medical therapies; however, as noted in our analysis, changes in diuretic therapy from baseline to 6 months did not account for the observed hemodynamic predictors of IASD efficacy. The magnitude of shunting was not assessed during exercise, which would have provided additional insight and is worth examining in future studies.

Conclusions

In the present HF patient population with EF >40%, both PCWP and CVP increased substantially during exercise, though the increases in PCWP were generally greater than those in CVP. After IASD implantation with an average Qp:Qs of 1.27, PCWP and CVP became more strongly correlated with each other, a consequence of the hemodynamic communication with left-to-right flow between the atria. The IASD significantly reduced the PCWP-CVP pressure gradient at rest and at peak exercise, a result of small increases in CVP and larger decreases in PCWP. Work- and weight-normalized PCWP decreased significantly after the IASD. There was variability in hemodynamic responses to IASD among patients, but, overall, there was a direct relationship between the peak exercise PCWP-CVP pressure gradient (ie, the driving force for left-to-right flow) and the reduction of peak exercise PCWP observed at 6 months. These findings may have implications for selection of patients most likely to exhibit a chronic beneficial hemodynamic response to IASD implantation. As expected, the greater the Qp:Qs, the greater the reduction in PCWP-CVP gradient. Further investigations into the variability of Qp:Qs across the population are also important. Findings were the same in the HFmrEF and HFpEF subpopulations.

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