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CLINICAL RESEARCH

First-in-Human Experience of Mechanical Preload Control in Patients With HFpEF During Exercise

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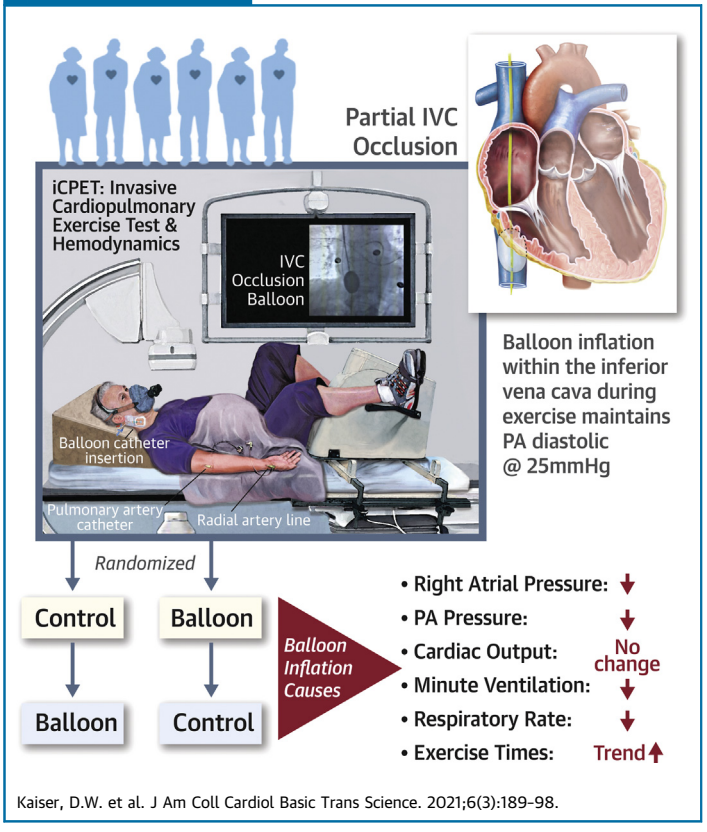
VISUAL ABSTRACT



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HIGHLIGHTS

- **Heart failure patients demonstrate pulmonary hypertension during exertion that correlates with limitations in exercise capacity.**
- **Titrated partial occlusion of the IVC through balloon inflation (mechanical preload control) during exercise significantly reduced PA pressure by 25% (from 68 ± 7 mm Hg to 51 ± 7 mm Hg) with no significant reduction in peak VO_2 (from 16.4 ± 5.8 ml/kg/min to 16.2 ± 4.0 ml/kg/min) or cardiac output (14.4 ± 5.9 l/min to 12.8 ± 2.9 l/min).**
- **Mechanical preload control trended toward longer exercise times and significantly reduced respiratory rate at matched exercise, suggesting that pulmonary pressures directly contribute to exercise limitations and hyperventilation in heart failure patients.**
- **Mechanical preload control may serve as a novel research and treatment strategy for heart failure patients.**

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

CPET = cardiopulmonary exercise testing

HFpEF = heart failure with preserved ejection fraction

LV = left ventricle/ventricular

IVC = inferior vena cava

PA = pulmonary artery

PCWP = pulmonary capillary wedge pressure

VCO_2 = carbon dioxide consumption

VO_2 = oxygen consumption

SUMMARY

Exercise intolerance remains one of the major factors determining quality of life in heart failure patients. In 6 patients with heart failure with preserved ejection fraction (HFpEF) undergoing invasive cardiopulmonary exercise testing, balloon inflation within the inferior vena cava (IVC) was performed during exercise to reduce and maintain pulmonary arterial (PA) pressures. Partial IVC occlusion significantly reduced PA pressures without reducing cardiac output. Partial IVC occlusion significantly reduced respiratory rate at matched levels of exercise. These findings highlight the importance of pulmonary pressures in the pathophysiology of HFpEF and suggest that therapies targeting hemodynamics may improve symptoms and exercise capacity in these patients. (J Am Coll Cardiol Basic Trans Science 2021;6:189–98)

During exercise, the average healthy individual can increase their cardiac output roughly 5-fold with only minimal changes in pulmonary arterial (PA) pressures (1,2). In contrast, patients with heart failure with preserved ejection fraction (HFpEF) demonstrate a rapid rise in right atrial pressure and pulmonary capillary wedge pressure (PCWP) during exercise, which correlates with limitations in exercise capacity (2–5). Numerous studies performed to date have used a variety of techniques to examine the mechanisms of exercise intolerance in patients with HFpEF and have identified both central factors (e.g., pulmonary pressures, cardiac output) and peripheral factors (e.g., oxygen metabolism, deconditioning) (6,7). However, while elevation in pulmonary pressures are associated with a reduction in exercise capacity, it is unknown if pulmonary pressures directly contribute to limitations in exercise capacity, or if pulmonary pressures are primarily a surrogate for reduced cardiac output (8).

We hypothesized that partial balloon inflation within the inferior vena cava (IVC) could reduce pulmonary pressures without compromising cardiac output. Prior work has demonstrated that heart failure patients can maintain cardiac output despite a reduction in filling pressures (9,10). Furthermore, during exercise, patients with HFpEF demonstrate a rapid increase in heart size that results in pericardial restraint that curtails the ability of the ventricles to increase stroke volume (11–13). Therefore, similar to diuretic therapy, partial IVC occlusion may be able to reduce pulmonary pressures, reduce pericardial restraint, and paradoxically maintain cardiac output at reduced filling pressures.

The objective of this proof-of-concept study was to provide initial evidence of safety and feasibility of transient, partial IVC occlusion as a novel therapy for heart failure patients. In addition, by uncoupling the relationship between pulmonary pressures and cardiac output, we sought to evaluate the effects of pulmonary pressures on respiratory parameters.

METHODS

STUDY POPULATION. Subjects who were referred for invasive cardiopulmonary exercise testing (CPET) at El Camino Hospital were considered for participation in this study. Subjects were required to be between 18 and 80 years of age with New York Heart Association functional class II or III heart failure symptoms. The left ventricular (LV) ejection fraction had to be >40% with at least moderate diastolic dysfunction on echocardiogram testing (defined as the ratio between the maximum velocity of the E-wave of mitral valve inflow to the maximal velocity of E >9).

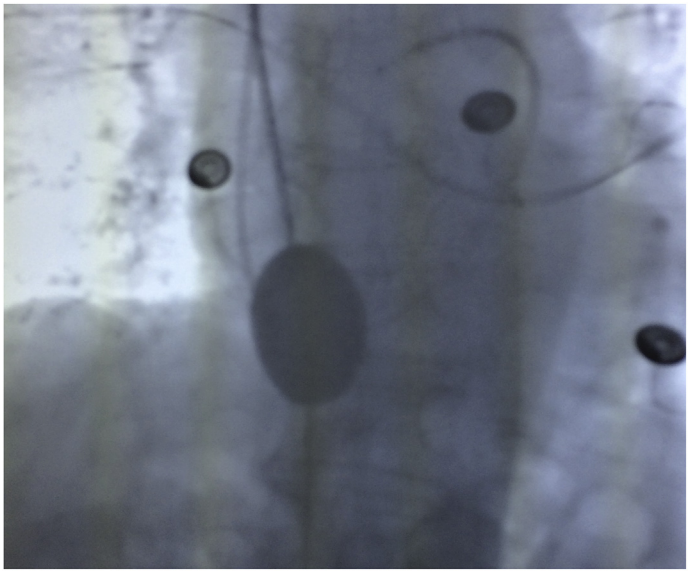
Subjects with an inability to lie flat, greater than mild valvular disease, myocardial ischemia, significant lung disease (prior chronic obstructive pulmonary disease diagnosis), resting or dynamic outflow tract gradient, severe pulmonary hypertension (>60 mm Hg at rest), greater than moderate right ventricular dysfunction, history of deep venous thrombosis or pulmonary embolism, pregnancy, recent (30 days) surgery or hospitalization, participation in another study, or advanced neurological disease were excluded from this study. The Institutional Review Board at El Camino Hospital approved this study.

STUDY PROCEDURES. The invasive CPET was performed in the catheterization laboratory under the supervision of 2 cardiovascular physicians at all times. Access was gained using ultrasound guidance and advanced under fluoroscopic guidance. A Swan-Ganz catheter was floated from the right brachial vein into the PA to measure intracardiac and pulmonary pressures. All pressure measurements were obtained through fluid filled catheters and then recorded, digitized (240 Hz), and stored for offline analysis. Pressures were taken at end-expiration as

the average of 3 beats. A 5-F catheter was placed into the radial artery to measure systemic blood pressure and allow sampling of arterial blood gases. Simultaneous venous blood samples from the Swan-Ganz catheter were obtained every minute during exercise. The invasive CPET was performed using a cycle ergometer using the Ultima Cardio2 MedGraphics Equipment (Medical Graphics, St. Paul, Minnesota) and linked to the BreezeSuite software package version 8.5 (Medical Graphics). Expired gas analysis was measured continuously throughout each phase of the study to measure minute ventilation, respiratory rate, oxygen consumption (VO_2), and carbon dioxide consumption (VCO_2). Cardiac output was then calculated by the direct Fick method.

In addition to standard right heart catheterization with exercise, we were able to control the filling pressure of the right ventricle. This was achieved by placing an intravascular balloon catheter (Coda Balloon; Cook Medical, Bloomington, Illinois) within the IVC (Figure 1). The catheter was placed from the right internal jugular vein and advanced into the IVC. A heparin bolus of 50 to 70 U/kg was given intravenously at the start of the procedure. During 1 of the 2 exercising studies, the occlusion balloon was partially inflated to reduce, and maintain, the PA diastolic pressure to 25 mm Hg. In 1 patient that did not demonstrate an elevation in pulmonary diastolic pressure during exercise, balloon inflation was performed to reduce PA diastolic pressure to 20 mm Hg. Patients were randomized to undergo balloon occlusion during either the first or second exercise studies. The patients were blinded as to the balloon's inflation status. Balloon inflation and deflation enabled real-time adjustment of right ventricular preload to control pulmonary pressures during exercise. The balloon catheter was inflated or deflated (unknown to the subject), and the subject was asked to proceed with incremental exercise on the cycle ergometer until symptom-limited. Invasive hemodynamic data, blood sampling, expired gas measurements, and ventilatory assessments were performed simultaneously at rest in the supine position and then during supine cycle ergometry exercise, starting at 0 W for 2 min and increasing in 10- to 20-W increments in 1-min stages until subject-reported exhaustion. After a 20-min resting period, exercise testing was repeated with the balloon occlusion inflated (if previously not inflated) or deflated (if previously inflated). The catheters were removed and the subject was monitored on the catheterization table for 10 min before returning to the progressive care unit. Participants were then monitored for at least 1 h prior to discharge.

FIGURE 1 Fluoroscopic Image of Partial IVC Balloon Occlusion



Fluoroscopic image of partial balloon inflation within the inferior vena cava (IVC) to control pulmonary pressures. The occlusion balloon was advanced from the right internal jugular vein so that the legs were free to cycle unencumbered.

STATISTICAL ANALYSIS. Continuous variables are expressed as the mean ± SD and categorical variables are presented as counts and percentages. For comparison at matched peak exercise, the time point the subject reached their peak value in 1 arm was used to determine the matched value during the second arm. For example, if a subject exercised for 30 s into stage 6 during the control arm, the hemodynamic variables for comparison for were chosen at the same time during the balloon occlusion arm—even if the subject exercised onto the next stage during balloon occlusion. Paired Student *t*-tests were used to compare continuous variables at matched peak exercise.

To compare hemodynamic variables across exercise stages, a 2-way analysis of variance was used with treatment arm and exercise stage as factors to account for repeated measurements. When analyzing hemodynamic variables across exercise stages for a single individual, Student's *t*-test with repeated measures was used. Significance was set a priori at $p < 0.05$. The data were analyzed using IBM SPSS Statistics version 22.0 (IBM, Armonk, New York).

RESULTS

A total of 6 subjects were enrolled and completed the study after providing informed consent. The baseline

TABLE 1 Baseline Demographics (N = 6)

Age, yrs	67.3 ± 6.3
Male	6 (100)
Body mass index, kg/m^2	31.4 ± 2.4
NYHA functional class	2.5 ± 0.5
Comorbidity	
Coronary disease	3 (50)
Diabetes mellitus	5 (83)
Hypertension	5 (83)
Atrial fibrillation	0 (0)
Laboratory measurements	
Creatinine, mg/dl	1.2 ± 0.3
Hemoglobin, g/dl	14.0 ± 1.1
Echocardiography parameter	
LV ejection fraction, %	52 ± 6
LV E/e′ ratio	12 ± 2
Medication	
ACE inhibitor/ARB	5 (83)
Beta-blocker	3 (50)
Loop diuretic	4 (67)
Hemodynamics (baseline)	
Heart rate, beats/min	77 ± 12
Central venous pressure, mm Hg	18 ± 6
Mean pulmonary pressure, mm Hg	29 ± 7
Mean arterial pressure, mm Hg	106 ± 9

Values are mean ± SD or n (%).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; E/e′ ratio = ratio of the peak early mitral inflow velocity (E) over the early diastolic mitral annular velocity (e′); LV = left ventricular; NYHA = New York Heart Association.

characteristics are demonstrated in Table 1. All subjects were male and over the age of 55 years. All patients had HFpEF, as confirmed by invasive hemodynamic measurement at rest (PCWP ≥15 mm Hg at rest) (14) and supported by an elevated exercise pulmonary artery systolic pressure ≥45 mm Hg in all patients (5). Most subjects had hypertension, had diabetes, and were obese. With the exception of 1 subject that demonstrated no elevation in PA diastolic pressure during exercise, in all other 5 subjects, the balloon was gradually inflated during exercise to maintain PA diastolic pressures at 25 mm Hg. Balloon occlusion was performed first in 3 subjects and second in the remaining 3 subjects. There were no trends in the data to suggest that the order of balloon occlusion made a significant difference.

Analyzing all subject data together, partial balloon occlusion significantly reduced pulmonary pressures, right atrial pressure, minute ventilation, and respiratory rate without a significant change in total oxygen consumption (VO_2) (Figure 2). Similarly, at matched peak exercise, partial IVC occlusion significantly reduced PA systolic and diastolic pressures ($p < 0.001$) and respiratory rate ($p = 0.003$). There was no significant difference in cardiac output ($p = 0.449$) (Table 2). In the subject without elevated PA diastolic pressure (who was the only patient to exercise to stage 9 in Figure 2), although it was unknown at the time, as the cardiac output increased, the partial balloon occlusion reduced cardiac preload and reduced the PA diastolic pressure to below the initial PA diastolic pressure. The reduction in PA diastolic pressure resulted in a drop in cardiac output (Figure 3). Interestingly, partial IVC occlusion did not appear to affect the subject's respiratory rate, despite a reduction in cardiac output. There was an increase in minute ventilation-to-VCO_2 ratio, driven by a reduction in VCO_2.

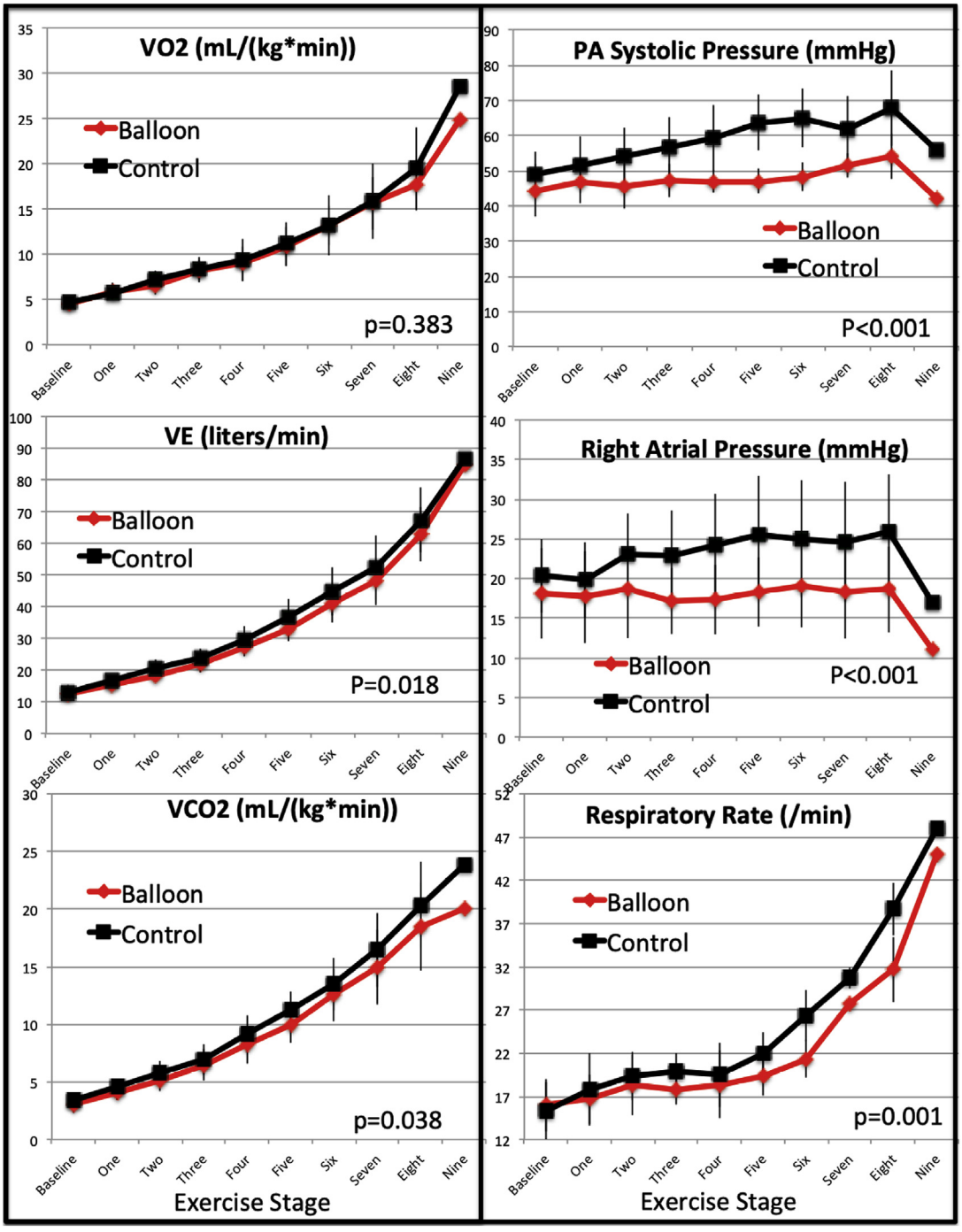
In general, partial balloon occlusion could reliably and rapidly control pulmonary pressures. When the IVC occlusion balloon was overinflated, there was a drop in PA diastolic pressures, likely causing a reduction in preload, and a transient reduction in cardiac output and VO_2. Underinflation caused the PA diastolic pressure to rise, resulting in pulmonary hypertension. Overall in all patients, partial IVC occlusion significantly reduced PA pressures ($p < 0.001$), the VO_2 was maintained, exercise times tended to be prolonged, and the respiratory rate was significantly reduced.

DISCUSSION

We report the first-in-human experience to mechanically control cardiac filling pressures in HFpEF patients during an invasive CPET. Our study demonstrated several key findings: 1) partial IVC occlusion can rapidly and significantly reduce right ventricular filling pressures and, subsequently, pulmonary pressures during exercise; 2) mechanical reduction of cardiac preload can reduce pulmonary pressures without reducing cardiac output; and 3) partial IVC occlusion during cycling in heart failure patients reduced respiratory rate at matched levels of exertion. These insights suggest a mechanical device that controls the preload to the heart may serve as a novel research and treatment strategy to understand and improve symptoms of dyspnea and exercise capacity in heart failure subjects. Further studies are warranted to assess mechanical control of preload in heart failure subjects.

This was the first study to mechanically control cardiac filling pressures during exercise. Previous studies demonstrated the safety of IVC occlusion at rest. The first report of balloon occlusion in the IVC to reduce filling pressures was performed by Eugene Braunwald in 1964 (9). Since then, partial balloon

FIGURE 2 **Invasive Cardiopulmonary Testing Data: Control Versus Partial IVC Occlusion**



Trajectories of oxygen consumption (VO_2), minute ventilation (VE), carbon dioxide consumption (VCO_2), pulmonary artery (PA) systolic pressure, right atrial pressure, and respiratory rate with and without partial inferior vena cava balloon occlusion during each exercise phase.

TABLE 2 Exercise Parameters With or Without Partial Inferior Vena Cava Balloon Occlusion in All Patients (N = 6)

	Balloon Occlusion	Control	p Value
Exercise time, min	9.5 ± 1.1	9.0 ± 1.2	0.068
Peak VO_2, ml/kg/min	16.2 ± 4.0	16.4 ± 5.8	0.863
Respiratory rate at matched peak exercise, breaths/s	29 ± 10	34 ± 9	0.003
Minute ventilation at matched peak exercise, l/min	55 ± 17	60 ± 16	0.004
Cardiac output at matched peak exercise, l/min	12.8 ± 2.9	14.4 ± 5.9	0.449
PA systolic pressure at matched peak exercise, mm Hg	51 ± 7	68 ± 7	0.001
PA diastolic pressure at matched peak exercise, mm Hg	24 ± 5	32 ± 7	0.007
Right atrial pressure at matched peak exercise, mm Hg	19 ± 5	25 ± 7	0.002
Heart rate at matched peak exercise, beats/min	122 ± 27	117 ± 17	0.413

Values are mean ± SD.
PA = pulmonary artery; VO_2 = oxygen consumption.

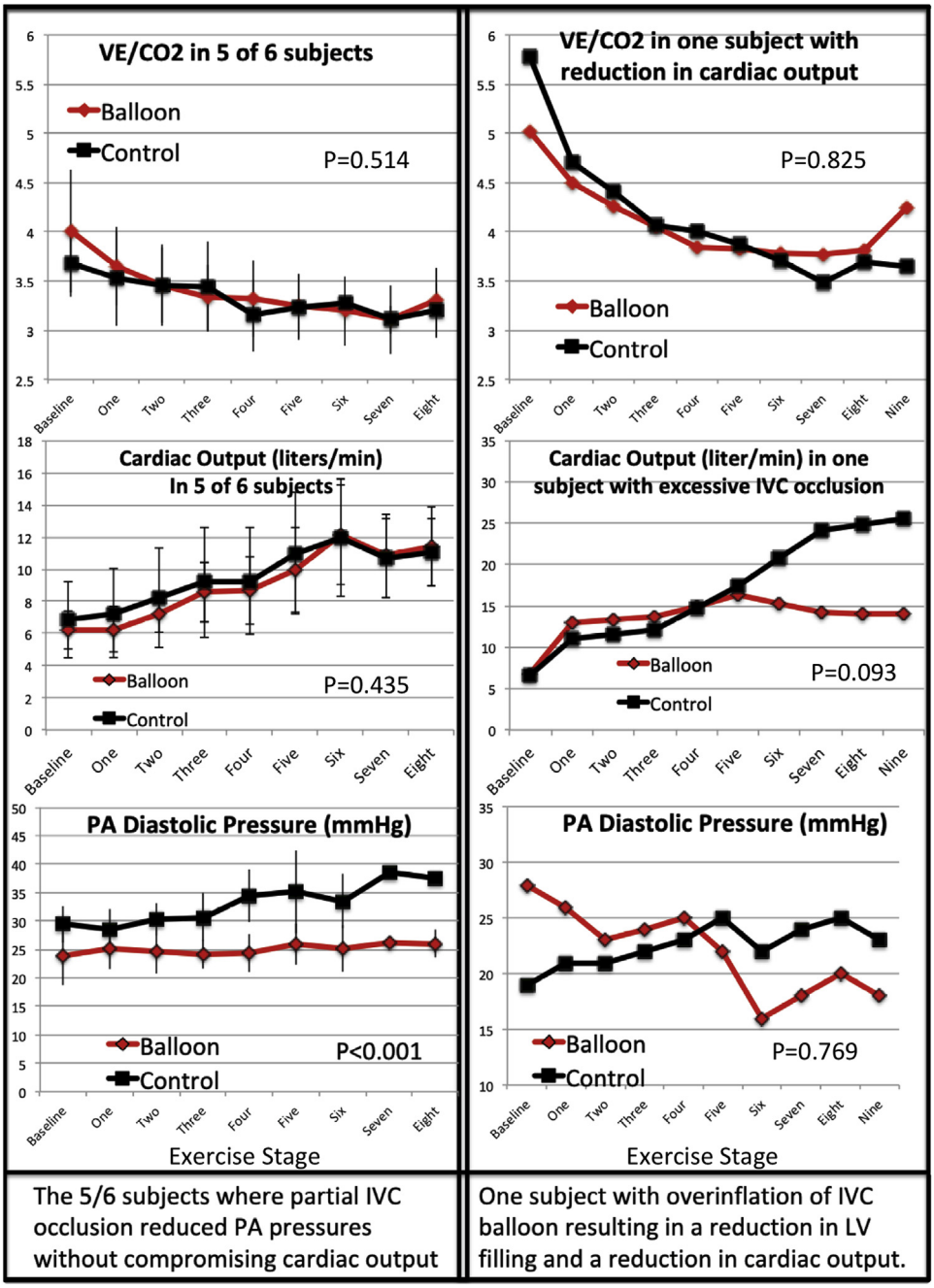
occlusion has been performed for creation of pressure-volume loops (15) and for controlled hypotension (16). The safety of this procedure has also been previously validated in patients with dilated cardiomyopathy (17). More recently, Kapur et al. (18) performed complete superior vena cava occlusion as a potentially new therapeutic approach to rapidly reduce cardiac filling pressures in subjects admitted with decompensated heart failure. These studies demonstrate that mechanical control of preload can rapidly and safely reduce pulmonary pressures. Because even medically and volume-optimized heart failure patients exhibit rapid elevations in pulmonary pressures and exhibit pulmonary edema during exercise (8,19,20), mechanical preload control may enable a new treatment strategy to delay pulmonary hypertension during exertion in heart failure patients to improve quality of life. The rapid feedback of mechanical control of cardiac preload is an attractive treatment option in the acute care setting when compared with medications, which cannot be titrated in real time to optimize blood pressures.

It seems counterintuitive that a pressure gradient within the IVC could reduce pulmonary pressures without reducing cardiac output, and seemingly impossible for this mechanism to improve cardiac output. However, there is growing evidence that the pericardium limits chamber enlargement during exercise and that rapid elevations in right heart filling pressures impair left ventricular function (11-13). The effective left ventricular distending pressure (the transmural pressure) that determines left ventricular stroke volume and cardiac output is the pressure within the LV minus the external compressive forces acting on the LV due to the right ventricle and pericardium (21). By reducing right ventricular filling pressures, partial IVC occlusion may reduce ventricular interaction during exercise and improve cardiac output (Figure 4). Because the right atrial pressure is a surrogate for pericardial pressure, the LV transmural pressure can be estimated as the difference between the PCWP and the right atrial pressure (13,22). However, in our study, PCWP was obtained at baseline but not during exercise. We did not perform intermittent balloon inflation to measure the PCWP, as we felt that inflating and deflating both the IVC occlusion balloon and the PA balloon catheter could be technically challenging and potentially dangerous without more experience. Future studies should consider incorporating PCWP in order to better understand LV filling pressures on cardiac output.

Our study suggests that rapid elevations in cardiac or pulmonary pressures directly contribute to hyperventilation. Heart failure patients demonstrate hyperventilation at rest and at exercise, which is generally felt to be secondary to altered ventilation and perfusion matching, ergoreflex overactivation, and increased chemosensitivity (23). In our study, neither the increased respiratory rate nor the increased pulmonary pressures resulted in significant changes to ventilation efficiency based on the unchanged ventilation and carbon dioxide (minute ventilation and VCO_2) relationships. Rather, the only change in the ventilation efficiency occurred in the patient with balloon overinflation, which likely reflects reduced blood flow to the ventilated lung (24). These data are consistent with the theory that pulmonary congestion may stimulate pressure receptors within the pulmonary vasculature, activate central respiratory motor activity, and result in shortness of breath (25,26). However, additional studies are needed to help elucidate drivers of ventilation during exertion in heart failure subjects. Controlling preload in exercising heart failure subjects does create a unique and valuable environment to better understand hemodynamic and physiologic relationships.

Other novel therapies aimed at treating pressure derangements in heart failure patients include pericardiotomy, splanchnic nerve blocks, and the interatrial shunt devices. Pericardiotomy mitigates the influence of right heart dilation from venous return on left heart filling pressures (27). A splanchnic nerve block attempts to reduce splanchnic autonomic and vascular tone, leading to redistribution of blood volume from the chest to the abdomen (28). The interatrial shunt devices are designed to improve exercise capacity by unloading elevated left atrial pressure by shunting blood to the right atrium (29). Despite their stark differences, each of these novel treatment modalities attempts to treat heart failure patients by

FIGURE 3 **Detailed Data in Selected Patients During Invasive Cardiopulmonary Testing**

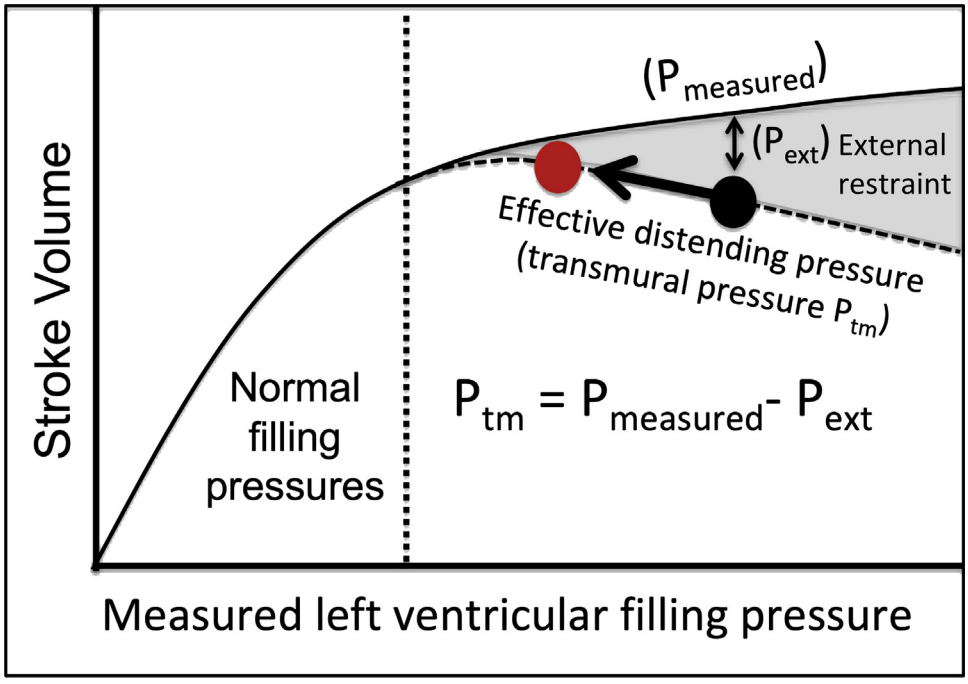


Trajectories of VE-to-VCO_2 ratio (VE/VCO_2), cardiac output, and PA diastolic pressure at each stage of exercise in 5 of 6 subjects with optimal left ventricular (LV) filling pressures **(left)**. The same trajectories in the 1 subject in whom overinflation reduced LV filling and a reduction in cardiac output **(right)**. IVC = inferior vena cava; other abbreviations as in Figure 2.

preventing pressure overload. Our study highlights the unique treatment opportunity of mechanical preload control to optimize cardiovascular hemodynamics using a closed-loop system.

A potential concern for mechanical preload control is the increased pressure behind the partial occlusion, which may impair organ function, cause lower extremity edema, or promote thrombus

FIGURE 4 Theoretical Effect of Partial IVC Occlusion to Reduce External Restraint and Paradoxically Improve Left Ventricular Stroke Volume



Theoretical relationship between LV filling pressures and stroke volume in heart failure subjects. The effective transmural distending pressure is the measured LV pressure minus external forces, typically the pericardial restraint ($P_{tm} = P_{measured} - P_{ext}$). Partial IVC occlusion may reduce pericardial restraint and paradoxically increase the transmural pressure and subsequently the cardiac output, despite reducing the measured LV pressure. Abbreviations as in Figure 3.

formation. Increased pressure behind the occlusion balloon is likely to decrease renal perfusion pressure, and may impair diuresis. Sustained balloon occlusion could lead to organ dysfunction, such as hepatic fibrosis (30). The amount of pressure rise will depend on total body blood volume, distribution of blood volume, and relationships between biventricular function (25). Combining preload control with an implantable pressure sensor to guide medical therapy may mitigate the need for sustained occlusion. Once the heart failure patient is euvolemic from medical therapy, a mechanical preload system can be used to optimize pulmonary pressures in the setting of acute volume shifts, such as those occurring during exertion. Additional studies are needed to better understand the relationship between mechanical preload control, organ function, and thromboembolic risk.

STUDY LIMITATIONS. First, our study was small in size. Larger studies are needed to demonstrate safety and corroborate our results. In particular, we limited our study to patients with preserved ejection fraction. Patients with reduced systolic function may be more sensitive to a reduction in filling pressures. In addition, our trial only included men, largely due to referral patterns for invasive CPET. Our next studies will incorporate both genders to make sure there are no important gender differences. Next, our study was relatively short in duration. It is unclear how preload control may affect filling pressures if left in place for longer periods of time. In addition, we performed both the control and balloon occlusion exercise studies on the same day in back-to-back sessions. While subjects were blinded to when the balloon was utilized and half of the subjects had the balloon occlusion study performed first, repeating the exercise study with only a 20-min resting period may have influenced the results. There was no significant difference in hemodynamic or respiratory parameters based on the order of balloon occlusion; however, none of the patients had undergone a CPET study, and patients may have had a learning effect, in which patients could have achieved a greater effort during the second exercise run.

Next, because we were focused on titrating the IVC balloon occlusion to pulmonary diastolic pressure, we did not perform PA balloon occlusion during exercise. Our next studies will include this to enable more detailed hemodynamic analyses. Finally, in order for a preload control system to improve exercise capacity in heart failure subjects for practical purposes, the system would need to be implantable and thus have significant engineering challenges, especially involving biocompatibility and device thrombosis concerns. These studies are currently underway and may enable revolutionary treatment options for heart failure subjects.

CONCLUSIONS

We report the first-in-human experience of using balloon occlusion within the IVC to mechanically control the preload of the heart during exercise in HFpEF subjects. We found that pulmonary pressures could be reduced without compromising cardiac output as long as the LV maintained adequate filling. Mechanical preload optimization caused a significant reduction in respiratory rate and a trend toward improved exercise times. This study demonstrates that mechanical control of cardiac preload may serve as a novel research and treatment strategy for heart failure patients.

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This study was funded by CardioFlow Technologies, which has intellectual property related to implanted devices to optimize heart failure outcomes. Dr. D. W. Kaiser, Dr. C. A. Kaiser, and Ms. Miyashiro own equity interest in CardioFlow Technologies. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Limitations in exercise capacity are a key hallmark of heart failure and are associated with significant elevations in pulmonary pressures during exertion. Here, we demonstrate the safety and efficacy of partial temporary balloon occlusion of the IVC to mechanically control the preload in heart failure patients to improve hemodynamic parameters during exercise. These findings highlight the importance of pulmonary pressures in the pathophysiology of HFpEF and suggest that therapies targeting hemodynamics may help improve symptoms and exercise capacity in these patients.

TRANSLATIONAL OUTLOOK: Mechanical preload control is a novel approach to control the rapidly changing hemodynamics seen in heart failure patients. This study demonstrated that partial IVC occlusion could reduce pulmonary pressures without compromising cardiac output. This study suggests that mechanical control of cardiac filling pressures may help treat pulmonary hypertension (and subsequently pulmonary edema) as a potential treatment strategy to improve exercise capacity and reduce hospitalizations in heart failure patients.

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