ABSTRACT

OBJECTIVES The purpose of this study was to provide insight into the potential for left atrium (LA) to aortic mechanical circulatory support as a treatment for patients with heart failure with preserved ejection fraction (HFpEF).

BACKGROUND Although HFpEF arises from different etiologies, 1 hallmark of all forms of this syndrome is a small or minimally-dilated left ventricle (LV). Consequently, the use of traditional mechanical circulatory support in end-stage patients has been difficult. In contrast, HFpEF is also characterized by a large LA.

METHODS Hemodynamic characteristics of 4 distinct HFpEF phenotypes were characterized from the published data: 1) hypertrophic cardiomyopathies; 2) infiltrative diseases; 3) nonhypertrophic HFpEF; and 4) HFpEF with common cardiovascular comorbidities (e.g., hypertension). Employing a previously-described cardiovascular simulation, the effects of a low-flow, micropump-based LA decompression device were modeled. The effect of sourcing blood from the LV versus the LA was compared.

RESULTS For all HFpEF phenotypes, mechanical circulatory support significantly increased cardiac output, provided a mild increase in blood pressure, and markedly reduced pulmonary and LA pressures. LV sourcing of blood reduced LV end-systolic volume into a range likely to induce suction. With LA sourcing, however, LV end-systolic volume increased compared with baseline. Due to pre-existing LA enlargement, LA volumes remained sufficiently elevated, thus minimizing the risk of suction.

CONCLUSIONS This theoretical analysis suggests that a strategy involving pumping blood from the LA to the arterial system may provide a viable option for end-stage HFpEF. Special considerations apply to each of the 4 types of HFpEF phenotypes described. Finally, an HFpEF-specific clinical profile scoring system (such as that of INTERMACS [Interagency Registry for Mechanically Assisted Circulatory Support]) would aid in the selection of patients with the appropriate risk-benefit ratio for implantation of an active pump. (J Am Coll Cardiol HF 2015;3:275-82)

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Heart failure with preserved ejection fraction (HFpEF) is an umbrella term that covers a relatively wide range of diseases with different underlying etiologies, pathophysiolgies, and constellations of comorbid conditions (1–3). Although there is no agreed-upon classification system for subdividing HFpEF patients, 1 system proposes 4 broad categories (Table 1). In addition to different chamber properties, these categories also segregate patients with different hemodynamic profiles. Regardless of etiology, patients with HFpEF have equally poor prognosis and quality of life as patients with heart failure and reduced ejection fraction (HFrEF). Although the prevalence and incidence of HFpEF is increasing (3), no study has yet proven a benefit from any specific treatment. Accordingly, patients with HFpEF have no evidence-based treatment options for persistent severe symptoms.

Left ventricular assist devices (VADs) have now been tested widely in end-stage HFrEF patients for bridge to transplant, bridge to decision, destination therapy, and bridge to recovery (4–6). However, there has been only limited experience with VADs in HFpEF (7–12). Some authors have even listed certain forms of HFpEF (e.g., hypertrophic cardiomyopathy [HCM]) as a contraindication for VAD therapy (13). The specific concern stems from the smaller left ventricular (LV) chamber sizes characteristic of HFpEF that can lead to obstruction of flow into the LV inflow cannula (7).

More recently, a micropump-based form of circulatory support has been introduced in which pump inflow is derived from the left atrium (LA), actively decompressing the LA and pulmonary circulation while improving systemic blood flow (The Synergy System, HeartWare International, Framingham, Massachusetts) (14). These features are particularly relevant for the HFpEF population, because a common feature of all forms of HFpEF is an enlarged LA. Other novel features of this micropump are that it is designed to be implanted in a subcutaneous pacemaker-like pocket (outside of the thorax), outflow is delivered to the subclavian artery, and the implant is via a minimally-invasive procedure. The pump is designed to provide partial mechanical support (2 to 4 l/min) and reduce LA pressure, and for HFrEF patients, the system is intended for use in INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) profiles 4, 5, and 6 (15).

The purpose of this study is to elucidate the theoretical hemodynamic effects of the Synergy System in patients with different forms of HFpEF using a previously-described cardiovascular simulation (16,17) that successfully predicted hemodynamic effects of Synergy use in HFrEF (14). Clinical considerations regarding when device implantation might be considered appropriate for an HFpEF patient are also discussed.

**METHODS**

**HFpEF PHENOTYPES AND BASELINE HEMODYNAMICS.** Four categories of HFpEF are listed in Table 1. Corresponding representative hemodynamic profiles are shown in Table 2. Type 1 HFpEF includes patients with HCM on the basis of inherited genetic mutation. Representative hemodynamics for this group were obtained from the subset of HCM patients reported by Kato et al. (18) who underwent heart transplant for intractable symptoms and had an LV ejection fraction (EF) ≥50%. Type 2 HFpEF includes patients with restrictive forms of cardiomyopathy, such as infiltrative diseases and endomyocardial fibrosis. One of the more common forms of type 2 HFpEF is amyloid cardiomyopathy. Representative hemodynamics for

<table>
<thead>
<tr>
<th>Table 1: Categories of HFpEF</th>
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<tr>
<td><strong>Type</strong></td>
</tr>
<tr>
<td>Type 1</td>
</tr>
<tr>
<td>Type 2</td>
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<tr>
<td>Type 3</td>
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<td>Type 4</td>
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**Table 1** Categories of HFpEF.

- **CAD** = coronary artery disease; **CKD** = chronic kidney disease; **CV** = cardiovascular; **DM** = diabetes mellitus; **HFpEF** = heart failure with preserved ejection fraction; **HTN** = hypertension; **LV** = left ventricular/ventricle; **LVH** = left ventricular hypertrophy; **MI** = myocardial infarction; **RV** = right ventricular.
TABLE 2 Representative Hemodynamic Parameters From Patients With Different Forms of HFpEF

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Type of HFpEF</th>
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<tbody>
<tr>
<td></td>
<td>Type 1</td>
</tr>
<tr>
<td></td>
<td>HCM</td>
</tr>
<tr>
<td>LV diastolic dimension (cm)</td>
<td>4.5</td>
</tr>
<tr>
<td>Septal dimension (cm)</td>
<td>1.6</td>
</tr>
<tr>
<td>Posterior wall thickness (cm)</td>
<td>1.6</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>64</td>
</tr>
<tr>
<td>Central venous pressure (mm Hg)</td>
<td>12</td>
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<tr>
<td>PA pressure (mm Hg)</td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>38</td>
</tr>
<tr>
<td>Diastolic</td>
<td>22</td>
</tr>
<tr>
<td>Mean</td>
<td>31</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>21</td>
</tr>
<tr>
<td>Ao pressure (mm Hg)</td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>110</td>
</tr>
<tr>
<td>Diastolic</td>
<td>70</td>
</tr>
<tr>
<td>Mean</td>
<td>83</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>3.3</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>1.9</td>
</tr>
<tr>
<td>PVR (Wood units)</td>
<td>2.3</td>
</tr>
<tr>
<td>SVR (Wood Units)</td>
<td>21.4</td>
</tr>
</tbody>
</table>

Data from Kato et al. (18) for type 1, Russo et al. (19) for type 2, and subsets of patients described in Burke et al. (21) for types 3 and 4. Values are mean ± sd for each of the 4 types of HFpEF. The effects of Synergy support on these hemodynamic conditions of the 4 types of HFpEF patients detailed in Table 2. These parameter value sets were arrived at by a custom-designed search algorithm to fit the hemodynamics for each of these conditions (21). In brief, this algorithm consists of a parameter search routine that simultaneously optimizes the match between target and model-simulated values of EF, cardiac output, central venous pressure, mean pulmonary artery pressure, pulmonary capillary wedge pressure, and aortic systolic, diastolic, and mean pressures, with equal weight given to optimizing the fit for all of these values. As a result, the model fits were very close to previously-published hemodynamic profiles for each of the groups. The key parameter values of the model are summarized in Online Tables 1 and 2. Please refer to the Online Appendix for definitions and values of all model parameters.

Aortic, pulmonary arterial, ventricular, and atrial pressure waveforms, as well as ventricular and atrial pressure-volume loops were constructed for each HFpEF type. The effects of Synergy support on these waveforms as well as on key hemodynamic parameters, especially LV end-systolic volume, were recorded. Simulations were performed with Synergy spanning the range from 20,000 to 28,000 rpm.

in HFpEF. Type 4 HFpEF includes patients with EF ≥50% and significant cardiovascular comorbid conditions usually including HTN plus (variably) coronary artery disease and prior myocardial infarctions who also had NYHA functional class III or IV symptoms. Type 4 patients typically have LV hypertrophy, which can manifest as concentric or eccentric hypertrophy (22); by definition, eccentric hypertrophy is associated with larger ventricular volumes, but still not as large as standard HFpEF. Representative hemodynamic data for this group were also obtained from a subset of patients in the study by Burke et al. (21) previously noted.
device. With the simulation set for Synergy inflow sourcing from the LV, the Synergy pump was ramped from 20,000 to 28,000 rpm (the maximum rate), which yielded a maximum flow rate of ~4 l/min, similar to or slightly less than flow rates reported to be used in RCM and HCM patients with full support VADs (e.g., HVAD [HeartWare]) (7). The simulation was then set to source blood from the LA, and rpms were ramped over the same range. The hemodynamic parameters included aortic and pulmonary arterial pressures, central venous pressure, pulmonary capillary wedge pressures (PCWPs), and total cardiac output (CO), which was the sum of flow from the LV and from the device.

RESULTS

The simulated hemodynamic effect of the MCS by Synergy viewed through the window of LV and LA pressure-volume relationships and loops in the prototypical patient with HCM is illustrated in Figure 1. At baseline (without MCS), HCM ventricular volumes are lower than normal both at end-diastole and end-systole, pressure generation is low-normal, and end-diastolic pressure is higher than normal (Figures 1A and 1C, pressure-volume loops in black). Note the end-diastolic volume of ~75 ml, compared with a normal value that would range between 100 to 150 ml. With Synergy inflow from the LV (Figures 1A and 1B), the LV pressure-volume loop loses its isovolumic phases, changing from a roughly trapezoidal shape to a more triangular shape. This is because with continuous flow MCS sourcing blood from the LV, the pump is continually withdrawing blood from the LV even when the aortic and mitral valves are closed; thus, volume is always decreasing except for the rapid filling phase that starts at the end of the would-be isovolumic relaxation phase when the mitral valve opens. There are RPM-dependent reductions in LV end-diastolic pressures and volumes. Most notably, although end-systolic volume increases slightly with increasing RPMs, there is a significant reduction in

![Simulated LA and LV Pressure-Volume Loops in HFpEF in Response to Mechanical Circulatory Support](image-url)
the minimum ventricular volume at the end of the would-be isovolumic relaxation phase, in this case down to \( \sim 20 \text{ ml} \). This reduction in minimum LV volume occurs even at the lowest pump flow rates. Importantly, in the current simulation, the pump in silico is not susceptible to obstruction until LV volume reaches \( 0 \text{ ml} \). When inflow is sourced from the ventricle, the chamber reaches very small volumes in all but the case of HFpEF in the setting of hypertension (HTN). HCM = hypertrophic cardiomyopathy; LVH = left ventricular hypertrophy; other abbreviations as in Figures 1A to 1C.

The effect of MCS with inflow from the LV also affects the LA mechanics (Figure 1B) by providing marked unloading, resulting in significant reductions in pulmonary capillary pressure and relief of pulmonary vascular congestion.

In contrast, MCS with inflow from the LA has a fundamentally different effect on the LV hemodynamics (Figure 1C) but similar effects on the LA (Figure 1D). RPM-dependent increases in systolic blood pressure and reductions in LV end-diastolic pressures and volumes, but increases in minimum LV volumes (which in this case coincide with LV end-systolic volumes), are demonstrated with LA cannulation. LA end-systolic volumes decrease, but not as dramatically as did LV end-systolic volumes with LV sourcing of pump inflow. In addition, the nature of the Synergy inflow cannula is such that it only protrudes \( \sim 2 \text{ mm} \) into the LA. For these 2 reasons, reductions in LA volume due to sourcing blood from the LA are not expected to result in cannula obstruction.

LV end-systolic volumes from the 4 types of HFpEF at baseline and during MCS with Synergy at 28,000 rpm with inflow cannula sourcing blood from the LV are summarized in Figure 2. As shown, simulations suggest small baseline LV end-systolic volumes in all forms of HFpEF except for the HFpEF-HTN (type 4 HFpEF) group, which is in the normal range. Accordingly, the predicted LV end-systolic volumes during MCS with LV inflow and Synergy at 28,000 rpm (pumping \( \sim 4 \text{ l/min} \)) are in the range of 20 to 30 ml, whereas LV end-systolic volume in the HFpEF-HTN heart is expected to be substantially larger. LV end-systolic volumes with inflow from the LA are significantly larger in all HFpEF groups, because there is less LV unloading with this approach.

**EFFECT ON CARDIAC OUTPUT.** With the partial MCS that the Synergy pump intends to provide, the total cardiac output is shared between the pump and the heart. As the speed of the pump is increased, pump flow increases and the intrinsic cardiac output decreases, as is evident from the pressure-volume loops of Figure 1C, which become progressively more narrow (i.e., decreased stroke volume) as rpms are increased. The effect of Synergy support at a speed of 28,000 rpm on intrinsic and overall cardiac output is summarized in Figures 3A to 3C. For these parameters, the effect of MCS is similar with LV or LA cannulation. There is slightly greater LV unloading with inflow from the LV, but pump flow and total CO were similar with the 2 approaches. Note that for HFpEF-HTN, baseline CO was within the normal range and increased to a supernormal range with MCS.

**EFFECT ON AORTIC AND PULMONARY PRESSURES.** The effect of MCS on other hemodynamic parameters is summarized in Figures 3D to 3F. There are significant decreases in pulmonary capillary wedge pressure that result in decreased pulmonary artery systolic pressure (despite the increase in CO), which are comparable for pump inflow from the LV and the LA. These trends were similar for pulmonary diastolic and mean pressures (data not shown). Aortic systolic pressure increased with MCS, but the increase was greater when the inflow was from the LA than from the LV. These trends were similar for aortic diastolic and mean pressures (data not shown). All of these trends depended on pump speed.
Note also that for the HFpEF-HTN, baseline aortic systolic pressure was higher than normal (by definition) and that this increased further during MCS, especially with pump inflow from the LA. Diastolic and mean aortic pressures increased similarly.

**DISCUSSION**

It is well established that patients with HFpEF have a prognosis similar to those of patients with HFrEF, especially if they have had a prior heart failure hospitalization. Currently, there are no proven therapies for HFpEF patients. Complicating matters is the fact that HFpEF is an umbrella term that encompasses different underlying diseases. Independent of the underlying disease, MCS would only be considered for HFpEF patients who have extreme symptoms and hemodynamic abnormalities, are unresponsive to standard medical therapies, and have a high rate of mortality (see the Clinical Considerations section). Despite different underlying cellular, molecular, and biochemical abnormalities, patients with Types 1, 2, and 3 HFpEF (Table 1) are particularly prone to the entire constellation of hemodynamic abnormalities addressed by conventional MCS, including elevated pulmonary capillary wedge pressure, low systemic arterial blood pressure, and low cardiac output (Table 2). These hemodynamic abnormalities can all be traced back to LV diastolic dysfunction, and result in signs and symptoms classically associated with diastolic heart failure. However, application of traditional MCS systems is difficult in these patients because of the small LV chamber size.

Topilsky et al. (7) reported the use of HeartMate II (Thoratec Corporation, Pleasanton, California) in patients with HCM (n = 4) and RCM (n = 4, amyloid or Fabry disease). It is noteworthy that, despite the fact that patients had reduced EFs (~20%), they all had small LV chambers. Nevertheless, compared with their experience in patients with traditional HFrEF, right atrial pressure increased more and cardiac output increased less during LVAD support in these HCM and RCM patients. They noted a high frequency (40%) of persistent right heart failure requiring prolonged inotropic support. It was speculated that this may have been due to primary involvement of the right ventricle in the underlying disease. It was most noteworthy, however, that in addition to challenges with device implantation due to the small LV, these patients experienced frequent “suck-down” events that made them difficult to manage. In another study, 3 HCM patients who were treated with HVADs had similar issues; 1 of these patients died at 3 months due to inlet obstruction leading to transient ischemic attacks and, ultimately, pump thrombosis resulting in cardiogenic shock (8).

Results of the present analysis suggest that use of the Synergy system with LA cannulation will result in similar hemodynamic benefits without the anatomical limitations seen in patients with contemporary LVAD technologies (24).

Patients with type 4 HFpEF (i.e., patients with common cardiovascular conditions such as HTN, coronary artery disease, myocardial infarction, diabetes, and so on) represent the most commonly encountered group of HFpEF patients. However, this group remains poorly characterized and is likely highly variable in terms of underlying pathophysiology (3,25). Stated differently, this is not a homogenous group of patients. Complicating development of therapies is the fact that a large percentage of
essentially normal in type 4 HFpEF patients (although, on average, resting cardiac output is by-case basis. An additional consideration is that such patients be considered for MCS on a case-namic effectiveness. For these reasons, it is prudent to pump could, in extreme cases, limit its hemody-
quired for pump-based devices. In addition, the high of anticoagulation and antiplatelet therapies re-
considered in these patients, especially in the setting further increase in blood pressure needs to be effect of MCS on PCWP, the potential effect of a Although there is a predicted, substantial bene
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tion is coupled to pulmonary afterload may
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tions. As summarized in Table 2, the resting PCWP of these patients was equally or more significantly elevated than in patients with the other types of HFpEF. These patients are also known to have rapid and dramatic further increases in PCWP with the onset of exercise, which would also be favorably affected by MCS. However, in comparison with the other types of HFpEF, these patients had significantly higher blood pressures and normal resting cardiac outputs; this is consistent with what we have iden-
tified in prior studies in different populations (2,26).

Although there is a predicted, substantial beneficial effect of MCS on PCWP, the potential effect of a further increase in blood pressure needs to be considered in these patients, especially in the setting of anticoagulation and antiplatelet therapies re-
quired for pump-based devices. In addition, the high pressure head against which the device would have to pump could, in extreme cases, limit its hemody-
amic effectiveness. For these reasons, it is prudent that such patients be considered for MCS on a case-
by-case basis. An additional consideration is that although, on average, resting cardiac output is essentially normal in type 4 HFpEF patients (Table 2), it is known that these patients have a significant limitation of cardiac output at peak exercise (27,28). Thus, the effect of MCS on cardiac output might prove beneficial during exertion.

One final factor to consider is the varying degrees of right heart involvement in the different forms of HFpEF. The degree to which right ventricular func-
tion is coupled to pulmonary afterload may determine the effect of LA decompression on RV mechanics and function. The model presented in this study suggests that MCS with LA unloading would reduce LV filling pressures and improve total cardiac output. Lowering the pulmonary venous pressure should translate to reduced RV afterload, whereas the improved cardiac output could increase RV preload that may worsen right-sided heart failure. However, it is important to note that the benefit on RV function after LA unloading in HFpEF may reflect the relative contribution of congestive versus impedance load on pulmonary artery pressure. Our current modeling does not account for the changes in the pulmonary vascular resistance, which take place after the reduction in the pulmonary venous congestive load has been achieved with me-
chanical unloading. Given the different prevalence and vasoreactivity of pulmonary HTN in patients with HFpEF (as compared with HFrEF), future studies will need to address the effect of LA decompression on right ventricular function in patients with advanced heart failure across the spectrum of HFpEF classification.

**CLINICAL CONSIDERATIONS.** Going forward, it will be important to also consider clinical factors that would render implantation of an MCS device appropriate for an HFpEF patient. For HFrEF, the INTER-
MACS profile score (15) has proven invaluable in capturing a patient’s prevailing health status and facilitating risk/benefit assessment. One approach would be to develop and validate an HFpEF-specific INTERMACS profile schema as suggested in Online Table 3. Another approach would be to use already-
available prognostic indicators that have been vali-
dated in the HFpEF population, such as the Kansas City Cardiomyopathy Questionnaire (29) or the MAGGIC score (30). This is a very important topic that is detailed further in the Online Appendix.

**STUDY LIMITATIONS.** The conclusions of the present study are subject to all limitations inherent in the use of a cardiovascular simulation, which have been noted previously (14). Nevertheless, the simulation has predicted the effect of other therapies, including the use of partial ventricular support in HFrEF (14) and the effect of surgical ventricular reconstruction (31).

**CONCLUSIONS**

There are several underlying diseases that result in HFpEF. Use of traditional MCS has the potential to normalize hemodynamics, but has been limited by anatomic constraints imposed by the small LV chamber. Use of a pump-based device that draws
blood from the LA has the potential to achieve the desired hemodynamic effects without such limitations. Varying degrees of HTN, right ventricular dysfunction, and pulmonary vascular involvement suggest that HFpEF patients should be considered for MCS on a case-by-case basis. In this regard, the current simulation, with further validation, might help to predict hemodynamic effects of MCS in individual patients and to guide therapy.

**REFERENCES**


**KEY WORDS** Heart failure with preserved ejection fraction, LVAD, mechanical circulatory support

**APPENDIX** For additional information regarding the cardiovascular model and supplemental tables, please see the online version of this article.