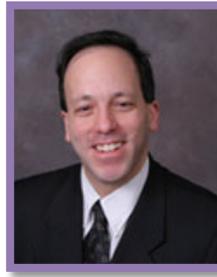




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REVIEWS:

Kilic A, Grimm JC, Whitman GJR et al. The survival benefit of simultaneous heart-kidney transplantation extends beyond dialysis-dependent patients. *Ann Thorac Surg* 2015; 99: 1321-1327.

The investigators conducted a retrospective analysis of patients included in the United Network for Organ Sharing (UNOS) Database who underwent simultaneous heart kidney transplantation (SHK) from 1992 to 2012. Specifically, they compared 5-year survival outcomes in these patients to those who underwent heart transplantation alone (HTA). Patients were stratified first by whether they required dialysis prior to transplantation; and among those who were dialysis independent, patients were stratified by the risk of requiring dialysis after transplantation.

The authors had previously derived and validated a renal failure risk score for requiring dialysis post transplantation, using patients listed in the UNOS database undergoing heart transplantation alone from 2000 to 2010. Using logistic regression analysis, the risk score incorporated recipient and donor characteristics such as recipient age, cause of cardiomyopathy, baseline creatinine clearance and serum bilirubin, BMI, presence of diabetes, need for mechanical ventilation, ICU level care or blood transfusions, donor age, ischemic time, and use of biatrial anastomosis. Survival outcomes in the present study were compared using Kaplan Meier analysis and multivariable logistic regression. The investigators also examined changes in the proportion of patients undergoing SHK from 1992 to 2002 (early era) and 2003 to 2012 (late era).

The study identified 665 SHK and 38,488 HTA patients. Fifty six percent of those patients who underwent SHK required dialysis pre-transplant. Dialysis independent patients with GFR <60 mL/min/1.73m² and high renal failure risk score comprised another 21% of all SHK performed. While only 2% of HTA patients required dialysis pre-transplant, 15% of HTA patients had both GFR <60 mL/min/1.73m² and high renal failure risk score. The fraction of SHK performed compared to all heart transplants increased from the early to late eras, but only by a factor of 1.5 in patients requiring dialysis and by 2.8 in the highest risk patients who were still dialysis independent.

Patients who underwent SHK were more likely to be African American and have diabetes. They were more likely to require blood transfusions while on the waiting list. There was no difference in age, gender and requirements for bridging with a ventricular assist devices, ICU level care or mechanical ventilation.

Dialysis independent patients at high risk of renal failure had higher 5-year survival rates with SHK compared to HTA (86% vs. 67%, $p < 0.001$). Similarly, patients already requiring dialysis prior to transplant had higher survival rates with SHK compared to HTA (69% vs. 54%, $p < 0.001$). There was no difference in survival outcomes for those patients with low renal failure risk scores who underwent either SHK or HTA. In all groups

of stratified patients, 1-year rejection rates requiring treatment were lower in patients undergoing SHK compared to HTA (14% vs. 37%, $p < 0.001$).

Despite better survival outcomes in patients with high renal failure risk scores or already on dialysis, the authors found that SHK transplantation was underutilized: only 305 out of 947 patients on dialysis prior to transplant and 116 out of 4,523 patients with high renal failure risk scores underwent SHK as opposed to HTA.

This study nicely complements earlier analyses of patients undergoing simultaneous heart and kidney transplantation. It provides not only data on survival in dialysis dependent and independent patients, but stratifies patients by risk of developing renal failure after transplant. Further, the authors also examine whether SHK are adequately utilized in this population. The chief limitations of this study include its retrospective nature and the lack of data on post transplant renal function, including the need for dialysis or repeat kidney transplantation.

Burkhoff D, Maurer MS, Joseph SM et al. Left atrial decompression pump for severe heart failure with preserved ejection fraction: theoretical and clinical considerations. *JACC Heart Fail.* 2015; 3(4): 275-282.

Burkhoff and colleagues¹ present an analysis of a new potential modality for the treatment of heart failure with preserved ejection fraction (HFpEF). This is an important paper for a variety of reasons. First, the use of mechanical circulatory support has not been widespread in patients with HFpEF who typically have normal or small ventricular dimensions and who can be particularly hard to manage in advanced stages. In addition, the simulation addresses the use of a new generation of “mini-VADS” exemplified by the HeartWare (formerly Circulite) Synergy pump in a new configuration. The authors describe the effect of “sourcing” the input to the pump from the left atrium as well as a traditional LV apical location. In addition, the authors lay out an interesting “INTERMACS”-like classification of HFpEF, which unfortunately is relegated to the appendix of the paper!

In terms of the simulation, Dr. Burkhoff has published prior analyses with this computer model, which has provided insight into other conditions. In this paper, the authors defined 4 distinct categories of HFpEF, and they specify parameters for the computer model, which are based on cited studies in humans. The figure below shows these categories. Type 1 is typical hypertrophic cardiomyopathy with genetically transmitted myocardial thickness and inherent diastolic dysfunction. Type 2 is infiltrative cardiomyopathy with the typical cause being amyloidosis. Type 3 is the unusual patient without thick walls but with diastolic dysfunction and symptoms. Lastly, Type 4 is the patient with classic HFpEF and various pre-disposing cardiac conditions such as hypertension, diabetes mellitus, prior infarcts, obesity etc. It is important to know that there is no consensus agreement on classification of HFpEF patients, but the formulation below seems quite reasonable.

Table 1: Categories of HFpEF

Type	Category	Key Features	Mechanism(s)	Cause of Heart Failure Syndrome
Type 1	Hypertrophic cardiomyopathy	Thick LV walls, small LV chamber	Genetic mutations	Diastolic dysfunction
Type 2	Infiltrative cardiomyopathies	Small chamber, generally have ↑ wall thickness, common to have RV involvement	Amyloid, sarcoid, hemochromatosis, endomyocardial fibrotic disease, etc.	Diastolic dysfunction, restrictive physiology
Type 3	Nonhypertrophic cardiomyopathy, without	Normal wall thickness, small or normal chamber size, no significant physiologic	Unknown (possible genetic abnormality)	Diastolic dysfunction (with or without

	significant CV disease (non-LVH)	stimuli for hypertrophy		restrictive physiology)
Type 4	1 or more underlying cardiovascular conditions	Varying combinations of HTN, MI, CAD, DM, CKD, obesity, etc.	Chronic neurohormonal activation, renal dysfunction, abnormal salt/water metabolism	Hypothesized to be due to volume overload state

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.

The computer model simulation of a HFpEF patient with a miniature blood pump (modeled after the Heartware Synergy) was explored with two inflow configurations (left ventricular inflow and left atrial inflow). The authors demonstrate that the hemodynamics improve with partial support from either LA or LV location of inflow but at the expense of LV size. The figure below from the paper shows that the left ventricular volumes in the hypertrophic cardiomyopathy and amyloid patients are predicted to be approximately 25 cc or less. This is likely to lead to ventricular suction and not a plausible mode of therapy for most such patients. Notwithstanding the reports of Park and others, most centers have not found utility in using conventional mechanical circulatory support in this setting. Current durable mechanical circulatory support devices cannot drain the left atrium and so the approach modeled in this paper cannot be reproduced with available devices.

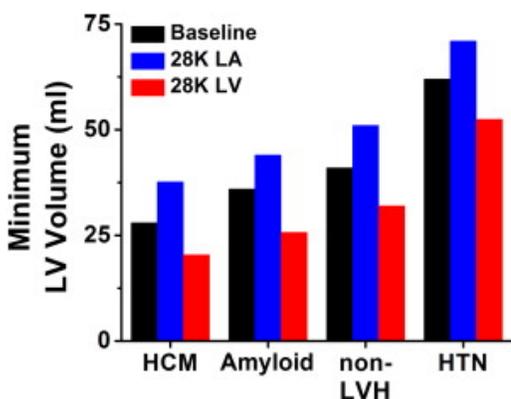


Figure 2: Effect of Mechanical Circulatory Support of End-Systolic Volume in Different Forms of HFpEF

Effect of mechanical circulatory support provided by the Synergy pump (HeartWare International, Framingham, Massachusetts) at 28,000 rpm in patients with different types of HFpEF on minimum LV volume comparing effects of sourcing inflow from the LV or the LA. 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 Figure 1.

The other very interesting part of this paper is actually hidden in the online appendix. The authors suggest that to move the field forward in regard to severe HFpEF, there should be a classification akin to the INTERMACS classification for HFrEF mechanical circulatory support. It is reproduced below. Once devices like the HeartWare Synergy or alternate devices for use in HFpEF are clinically available, classifications such as this will be critically important.

Online Table 3: Proposed modifications to INTERMACS profiles for HFpEF.

Profile	HFpEF
1	Cardiogenic Shock. Hospitalization with invasive hemodynamic measurements demonstrating low cardiac output and elevated cardiac filling pressures associated with a normal ejection fraction. Requires evidence of end-organ dysfunction.
2	Recurrent Advanced HFpEF. Requires current hospitalization with at least 2 prior hospitalizations in the past 6 months for HFpEF. Patient should have manifest volume overload with abnormal end-organ function.
3	Signs and Symptoms at rest including nocturnal dyspnea, persistent edema, elevated neck veins, and inability to diurese without azotemia (e.g., BUN<50% greater than upper limit of normal). Frequent clinic visits without hospitalizations in the past 12 months.
4	Exertion intolerant
5	Exertion limited
6	Class III Symptoms

In summary, Burkhoff and colleagues present a window onto the potential future of treatment for severe diastolic dysfunction and potentially someday a way to provide a mechanical circulatory support option for eligible patients waiting for transplantation with diseases such as amyloid and restrictive cardiomyopathy. Further attention should be paid to ways to create controlled left atrial to right atrial shunts as recently described by Søndergaard et al² and analyzed theoretically by Kaye and Burkhoff.³

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