Heart failure with Preserved Ejection Fraction; learning from failure

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Heart failure with preserved ejection fraction (HFpEF) has been a vexing disease for internists, cardiologists and geriatricians. The high prevalence and lack of evidenced based therapies makes management of this syndrome very challenging for both clinicians and patients. A number of clinical trials have applied treatment paradigms that have been successful in treating heart failure with reduced ejection fraction (HFrEF). Unfortunately, therapies centered on neuro-hormonal blockade have no benefit on morbidity or mortality in HFpEF. The reasons for the lack of benefit are not entirely clear but likely reflect the vastly different pathologic remodeling that occurs with the heart. This review will identify gaps in our current understanding of the epidemiology and patho-physiology in HFpEF as well as preview future directions for HFpEF therapy. At the conclusion of this lecture, the listener should be able to:

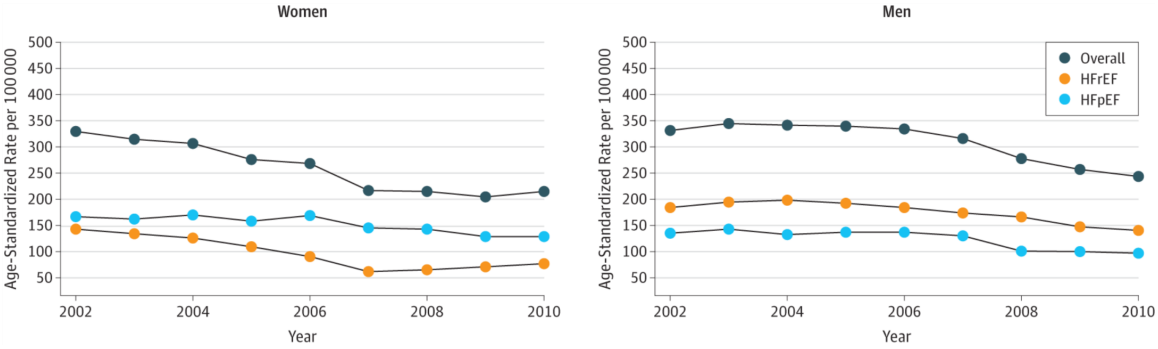
1) Characterize the differences in ventricular remodeling between HFpEF and HFrEF
2) Describe the factors that lead to increased arterial and ventricular stiffness
3) Understand the numerous diagnostic dilemmas and pitfalls for diagnosing HFpEF
4) Describe the rationale for using nitrates in the management of HFpEF exercise intolerance

Heart failure (HF) affects almost 6 million patients in the US and is growing in prevalence. (Roger et al., 2011) The majority of patients diagnosed with HF have depressed systolic function though a significant number of these patients, between 30 to 50%, have relatively preserved ejection fraction (HFpEF) at rest and suffer similar mortality and re-hospitalization rates as those with depressed EF. (Bhatia et al., 2006; Fonarow et al., 2007; Owan et al., 2006) Unlike HF with reduced ejection fraction (HFrEF), to date no evidence-based intervention has improved survival or quality of life in such patients. Traditional targets of the cardiovascular system, e.g. neuro-hormonal blockade, have failed to improve mortality or reduce HF symptoms and exacerbations. Other therapies targeting myocardial fibrosis and stiffening, elevated pulmonary vascular pressures and chronotropic incompetence have shown limited or no efficacy. (Edelmann et al., 2013; Kass et al., 2010; Redfield et al., 2013) Very little progress has been made over the past two decades in treating a disease that has increased in prevalence and that has similar morbidity and mortality as patients with heart failure with *reduced* ejection fraction. This review will cover the epidemiology and patho-physiology in HFpEF as well as gaps in current understanding and future directions for HFpEF therapy.

Epidemiology

HFpEF now accounts for nearly half of all heart failure hospitalizations. With the increased use of echocardiography in the clinical setting in the early 1970s, a number of heart failure patients were noted to have "normal" systolic function. Initially defined as *diastolic* heart failure, the prevalence of this syndrome increased gradually in the subsequent decades in contrast to heart failure with *reduced* ejection fraction, which has

remained relatively stable. More recent data however show that in the United States, the rates for heart failure have declined over the past decade (figure). Although the declines were driven primarily by lower incidence of HFrEF, rates for HFpEF also were also lower.



Heart failure incidence in Olmsted County, Minnesota from 2002 through 2010. Rates of heart failure have slowly declined over this time period largely driven by declines in heart failure with reduced ejection fraction. HFpEF rates have also declined slightly suggesting better management of stage A or "at risk" patients. (JAMA Int Med 2015)

The prognosis for patients with HFpEF differs from those with HFrEF. Patients with HFpEF have much lower rates of heart failure hospitalizations as well as death from cardiac causes. Nearly half of deaths in HFpEF are from non-cardiac causes while for HFrEF nearly two-thirds of deaths can be attributable to cardiac disease. One likely explanation for this difference in morbidity and mortality may be due to the high burden of co-morbid conditions in HFpEF. HFpEF patients are more likely than HFrEF patients to be older, more predominantly hypertensive, more likely to have renal impairment, atrial fibrillation as well as higher rates of non-cardiac diseases including chronic lung diseases, cancer, anemia and hypothyroidism. (Bursi et al., 2006)

The high preponderance of co-morbid conditions has driven a push to characterize HFpEF into distinct "phenotypes" based on the presence of distinguishing co-morbidities. The rationale for this approach is that differences in cardiac risk burden likely affects the

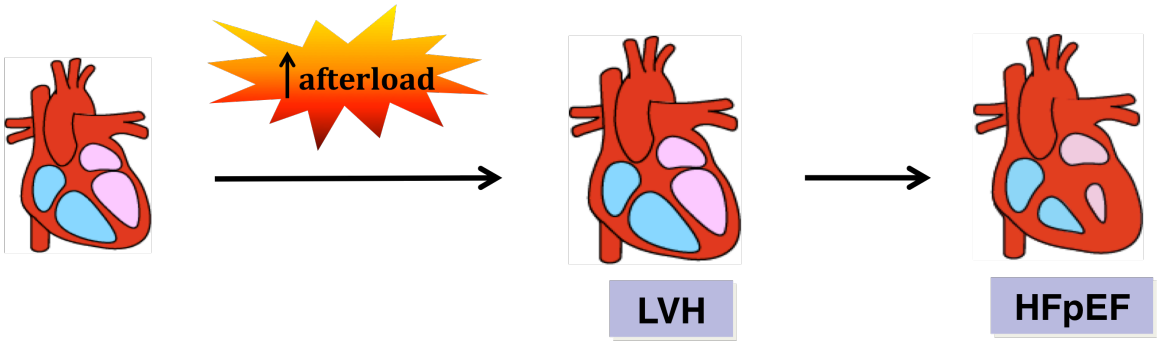
progression of heart failure. For example, a HFpEF patient with diabetes may be more likely to have micro-vascular dysfunction and autonomic dysfunction compared to a HFpEF patient with malignant hypertension and left ventricular hypertrophy alone. By splitting the syndrome into distinct phenotypes by co-morbid conditions, a complex clinical syndrome can be approached and characterized in a reductionist and possibly clearer manner.

However this approach ignores the observation that HFrEF patients often have a similar number of co-morbid conditions as those with HFpEF. A number of the purported unique HFpEF phenotypes can also be observed in HFrEF (e.g. atrial fibrillation, obesity, diabetes, hypertension, etc.). HFrEF patients also have many of the same clinical markers such as endothelial dysfunction, pulmonary hypertension as well as chronotropic incompetence as seen in HFpEF. Thus efforts to characterize the HFpEF syndrome by its non-cardiac phenotype ignore the elephant in the room, namely impaired diastolic relaxation and cardiac stiffness.

HFpEF Phenotype

In order to define the HFpEF phenotype, it is important to understand the differences between HFpEF and HFrEF physiology. One of the most notable differences between these types of heart failure is the type of ventricular remodeling that occurs. HFrEF is typically characterized by a dilated and thinned left ventricle while left ventricular remodeling in HFpEF can range from subtle decreases in ventricular size and slight increases in wall thickness to an overtly hypertrophied myocardium.

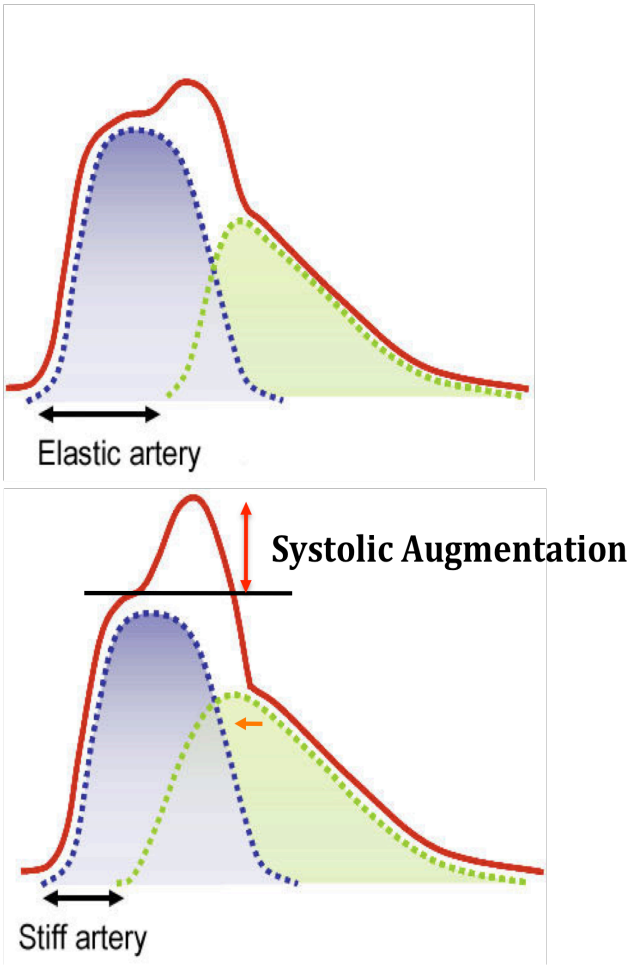
The initial insult leading to ventricular hypertrophy and increased stiffness is not known but thought to arise from arterial stiffening and may explain why the syndrome is more common amongst the elderly and women. Arterial stiffening occurs with healthy aging but can be accelerated by the presence of co-morbid conditions such as diabetes. Women are also more likely than men to develop increased arterial stiffness which may explain their higher likelihood for developing HFpEF. (Coutinho et al., 2013)



Presumed model for development of HFpEF from an unaffected myocardium. Overtime, increased arterial afterload leads to increased ventricular hypertrophy (LVH). The factors affecting the transition from LVH to HFpEF are unknown.

Afterload is the load or pressure against which the ventricle contracts. Often confused with blood pressure, afterload represents the summation of a number of components of the peripheral vascular network that feedback to produce ventricular impedance. The components of afterload are typically modeled by a three element Windkessel model which simulates the varying hydraulic load on the heart by incorporating arteriolar resistance, a capacitance element simulating the elastic potential energy of large arteries and characteristic impedance of the aorta representing the resistance provided by blood in the proximal aorta. Blood pressure whether central aortic or brachial, is a function of the interaction of these elements in conjunction with the contractile energy of the heart.

Arterial stiffening effects afterload by changing both elastic potential energy stored in large artery wall as well as arteriolar resistance. The end result of increased arterial stiffness is to increase wave transmission and reflection within the circulatory system. As with any hydraulic system, the ejection of blood from the ventricle during systole delivers an impulse of blood into the circulatory system. This generates a pulse wave that can be seen in any arterial waveform tracing. As the wave propagates throughout the circulation, reflected waves form at bifurcations of the arterial system. These reflected waves, if timed properly can actually meet the forward impulse generated by cardiac contraction and even further augment the systolic wave.



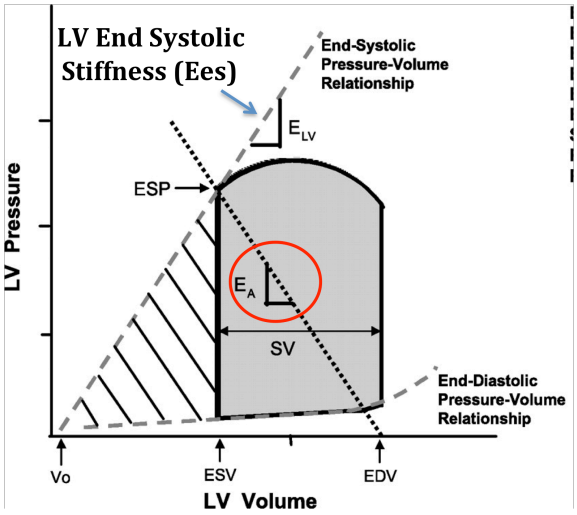
Examples of wave reflection (green shade) in the setting of an elastic or stiff artery. In a stiffer blood vessel, the wave reflection arrives earlier during systolic ejection resulting in systolic blood pressure augmentation. The early arrival of the reflected wave also transmits increased afterload to the ejecting ventricle. (Figure from Complior.com)

The speed of the backward wave reflected wave depends on the degree of arterial stiffening. Imagine sound transmission through a stiff metal tube versus a softer, elastic rubber tube. Sound waves travel much more quickly through the dense metal than the soft elastic material of rubber. A similar concept can be applied to the human vascular system. The figure to the left shows an example of an elastic artery and stiff artery. The initial upstroke is shaded in purple and similar for both. The green shade is the reflected

wave and can be seen on an arterial waveform tracing as the dichrotic notch. In the stiff artery, the reflected wave arrives just milliseconds earlier compared to the elastic artery (orange arrow in lower panel). This early arrival of the reflected wave meets the remnants of the systolic wave. The additive wave produces a higher systolic wave and is termed the systolic augmentation. This increased systolic pressure is in turn transmitted back as increased afterload.

The measurement of arterial stiffness can be cumbersome in a clinical setting. There is an easier way to estimate afterload, namely **arterial elastance (Ea)**.(Kelly et al., 1992) Calculated as Systolic Blood Pressure/Stroke Volume, arterial elastance represents an integrated measure of effective arterial afterload. Conceptually, as afterload (Ea) increases, systolic blood pressure increases if the left ventricle is able to maintain stroke volume. If the ventricle is unable to augment systolic blood pressure in response to high afterload, stroke volume will decrease.

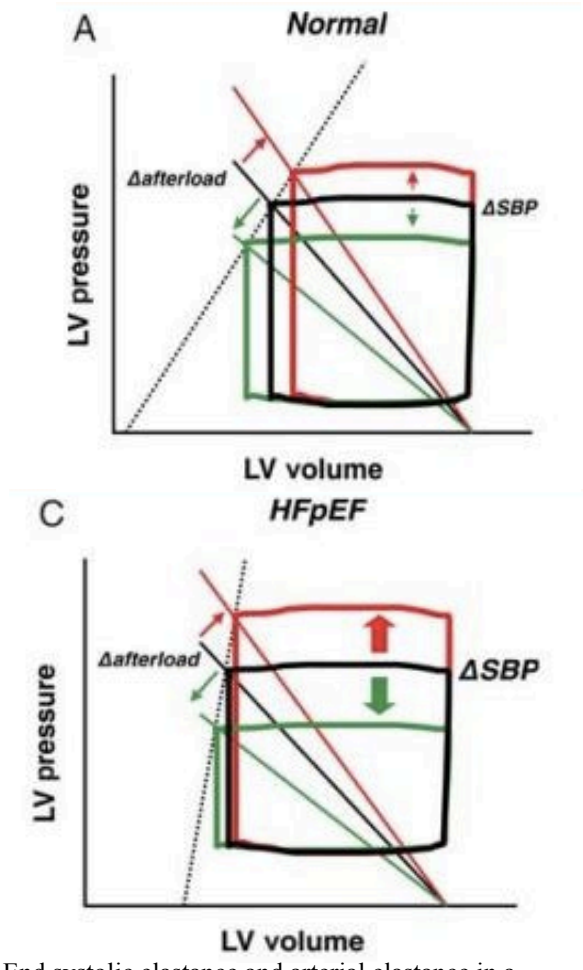
Over time, the left ventricle will adapt to persistent increases in afterload by either increasing wall thickness or by decreasing ventricular size. Following LaPlace's law, that tensile force is proportional to chamber radius, a smaller sized ventricle will have lower



tensile (i.e. wall stress) compared to a larger ventricle under the same afterload pressure. The end result is that ventricular elastance (Ees), or stiffness, increases with chronic exposure to high arterial afterload (Ea). The ventricle must increase its end contractile stiffness in order to match an

increased afterload in order to preserve stroke volume.

The relationship between arterial afterload and ventricular stiffness can be demonstrated on the pressure volume loop as seen in the figure above. The intersection of the Ea slope and the ventricular elastance (Ees) slope represents **ventricular-arterial coupling**. Changes in this intersection point result in changes in stroke volume. For example, if Ea (afterload) decreases (green line in figure below), then stroke volume (green box in figure below) increases assuming ventricular elastance or contractility remains the same. Conversely, if afterload increases (shown by red line in figure below), stroke volume decreases.



End systolic elastance and arterial elastance in a normal and HFpEF ventricle. Changes in afterload in a ventricle with increased end systolic elastance (steeper slope; bottom panel) result in minimal changes in stroke volume. (Borlaug et al; Euro J Heart Failure 2010)

In a HFpEF ventricle (lower panel), increased end systolic elastance changes the ventricular-arterial coupling relationship such that changes in afterload have little effect on stroke volume. In the lower panel, increasing (red line) or decreasing (green line) arterial elastance has minimal effect on stroke volume changes. The increased ventricular elastance or stiffening, again, is a result of chronic increases in afterload and leads to both systolic and diastolic stiffening of the ventricle.

The high LV chamber elastance also helps explain why vasodilators are of limited

benefit in HFpEF patients. Changes in Ea lead to sharp drops or increases in end-systolic pressure with very little change in stroke volume. This highly labile blood pressure fluctuation in response to changes in afterload is in stark contrast to patients with HFrEF.(Schwartzenberg et al., 2012) HFrEF patients, because of low Ees, have small changes in arterial pressure and much larger increases in stroke volume after vasodilator administration highlighting the fundamental differences in cardiac physiology between these two types of heart failure.

The consequences of increased ventricular stiffening are most evident during physical exertion or exercise. Stroke volume reserve is diminished as a result of inefficient ventriculo-arterial (VA) coupling.(Borlaug and Kass, 2008) As described earlier, at rest VA coupling calculated as the ratio of arterial and end systolic elastances (Ea/Ees), is comparable to age matched controls due to similar elevations in arterial and ventricular stiffness.(Kawaguchi et al., 2003) In a healthy individual, Ees increases with exercise while Ea remains the same or decreases leading to a fall in the coupling ratio. A low Ea allows for a relatively large increase in stroke volume but in patients with HFpEF, high baseline arterial stiffness in conjunction with high ventricular elastance limits stroke volume responsivness(Tartiere-Kesri et al., 2012) which in turn affects aerobic performance.(Kitzman et al., 2013)

In addition to limitations in exercise stroke volume reserve, as cardiac stiffness increases the ventricle becomes less distensible during diastole, where for a given volume end-diastolic pressure is higher.(Prasad et al., 2010) During exercise, when preload and heart rate are both elevated, the decrease in distensibility in conjunction with impaired

lusitropy lead to rapid rises in pulmonary filling pressures with pulmonary capillary wedge pressure sometimes approaching 40 mmHg.

The factors leading to a slowly relaxing and less distensible ventricle are not completely understood. Aging, hypertension and obesity are common precursors to HFpEF but likely affect ventricular function through different mechanisms. Aging is marked by reductions in ventricular relaxation and diastolic suction.(Popovic et al., 2006) Many elderly individuals are misclassified as having HFpEF on the basis of decreased tissue Doppler relaxation patterns. These characteristics are independent of fitness status and co-morbid conditions; even elite senior athletes who are otherwise healthy and have large compliant ventricles exhibit myocardial tissue relaxation patterns similar to sedentary age-matched controls.(Carrick-Ranson et al., 2014) In contrast, hypertension and obesity independently lead to changes in *both* ventricular morphology as well as functional changes in diastolic tissue relaxation.(Lauer et al., 1991; Mogelvang et al., 2009; Russo et al., 2011) Patients with hypertension or obesity have increased LV mass, decreased diastolic recoil and diminished diastolic relaxation. Thus the interaction between aging and its associated impairments in lusitropy, in conjunction with hypertension and obesity related ventricular hypertrophy and end-diastolic stiffness results in a unique cardiac phenotype at risk for the development of HFpEF.

Diagnostic Dilemma

One of the major challenges in understanding the HFpEF phenotype and its primary physiologic abnormalities is accurately identifying patients who actually have HFpEF. In many ways, the initial labeling of HFpEF as diastolic heart failure has shifted

the burden of diagnosis on to echocardiography, a modality that can "assess" diastolic function. Findings on echocardiography that are suggestive of diastolic or relaxation abnormalities are decreased tissue Doppler velocity, prolonged ventricular relaxation times (isovolumic relaxation time – IVRT) as well as mitral inflow velocity. Taken as a whole, these abnormalities are critical components in defining the degree of diastolic dysfunction.

Unfortunately, diastolic parameters assessed by echocardiography are highly influenced by pre-load do not necessarily reflect diastolic "function" but rather volume status of the patient. Highlighting this point, many of the diastolic abnormalities seen in HFpEF are also seen in HFrEF. As left atrial pressure increases, early mitral inflow increases, propagation velocity both increase and IVRT may shorten. Progressive increases in grades of diastolic function (e.g. grade 1, 2 or 3) reflect increased preload and not necessarily abnormalities in diastolic relaxation or increased myocardial stiffness.

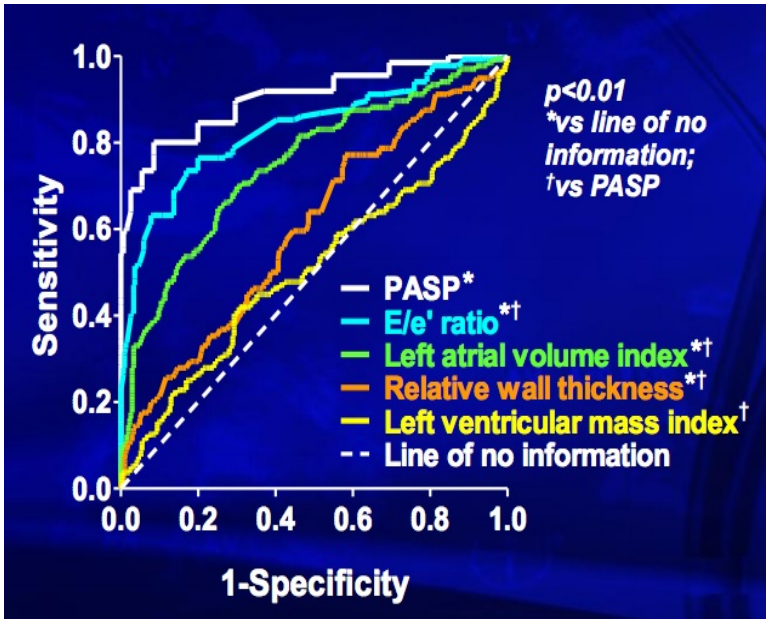
In addition tissue Doppler velocities, which are one of the key markers of a slowly relaxing ventricle can be low under normal healthy aging. As noted earlier, older patients or those with hypertension and obesity can have echocardiographic findings that could be consistent with HFpEF. While HFpEF is ultimately a clinical diagnosis, many of the tools used in diagnosis (echocardiography, serum B-type natriuretic peptide, functional testing) can be confounded by non-cardiac co-morbidities.

The lack of a gold standard test for HFpEF makes it possible to both over-diagnose and under-diagnose the syndrome. By joint European Society and American Heart Association guidelines, the diagnosis of HFpEF requires essentially three elements:

1) Symptoms of heart failure or hospitalization for heart failure

2) Abnormal diastolic function by echo
3) Objective evidence of elevated cardiac filling pressures (invasive or serum biomarker)

The criteria are specific but may miss patients who do not have over symptoms of heart failure. Only about one-third of HFpEF patients present with lower extremity edema. (Zile and Brutsaert, 2002) And since the symptoms mostly occur with exertion, many patients have consciously or unconsciously limit their physical activity to minimize symptoms. In these instances, echocardiography can be useful to identify "sub-clinical" HFpEF. As shown in the figure below, an elevated pulmonary artery systolic pressure (estimated from a regurgitant jet from the tricuspid valve) and increased left atrial volume adds further highly specific and sensitive information regarding increased cardiac filling pressures that is age and co-morbidity independent.



Independent prognostic factors for diagnosing HFpEF (Lam et al; JACC 2009)

The implications for an accurate diagnosis can be seen in early to even recent HFpEF trials which recruited patients on the basis of heart failure symptoms including dyspnea on exertion. In the Aldo-DHF study, a randomized trial assessing the efficacy of spironolactone on diastolic function and exercise capacity, almost 80% of enrolled

participants had grade 1 (or age appropriate) diastolic "dysfunction" and nearly all had normal left atrial volumes suggesting minimal to no evidence of increased cardiac filling pressures. One wonders if many of the negative trials in HFpEF were the result of medication inefficacy or inaccurate study subject diagnostic criteria.

Therapeutic Pathways and Interventions

The HFpEF literature is littered with failed trials. To date, no therapy has proven to be effective in reducing a variety of clinical end points including death, re-hospitalization, change in echocardiography parameters or improvement in functional capacity. Small studies of aerobic exercise intervention has been shown to be beneficial in improving functional capacity and quality of life but with no change in underlying cardiac and diastolic function.(Pandey et al., 2015)

Ultimately a successful therapy needs to reverse the two primary pathophysiologic abnormalities discussed earlier: 1) increased ventricular and arterial stiffening and 2) excessive increase in cardiac filling pressures with low level exertion. Strategies to reverse ventricular stiffness have primarily focused on myocardial fibrosis. It is still unclear if the increased passive stiffness is due to increased fibrosis(Mohammed et al., 2015) or rather changes in myocardial diastolic tension mediated via abnormal phosphorylation states of large basement membrane proteins (e.g. Titin). (Zile et al., 2015)

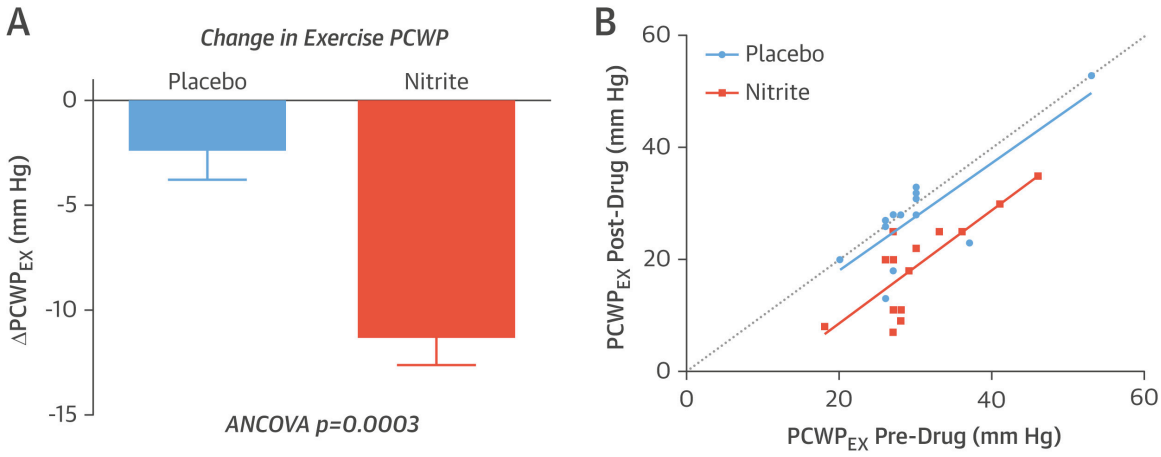
Spironolactone has become a popular study medication given the impressive effects of mineralo-corticoid antagonists on scar and fibrosis formation immediately post myocardial infarction and dilated cardiomyopathy. There have been a number of studies

of spironolactone and HFpEF but the largest study to date assessing the effect of spironolactone on heart failure re-hospitalization and death was TOPCAT. (Pitt et al., 2014) In nearly 3400 HFpEF patients (EF>45%) randomized to spironolactone or placebo, there was no difference in the event rate for the composite primary outcome of death or re-hospitalization. When analyzed by geographical location, patients from North America/Europe fared better than those in Russia/Georgia. Event rates were from Russian and Georgian patients was very low suggesting many of these patients were mis-diagnosed HFpEF subjects. Interestingly in another sub-group analysis stratified by ejection fraction, patients with ejection fractions less than 55% benefited from spironolactone more so than those with ejection fractions greater than 55%. This differential effect driven by ejection fraction brings up another dilemma for the characterization of HFpEF, mainly what is a normal ejection fraction.

Strategies to combat excessive rises in cardiac filling pressures have also had limited success. Ongoing studies have focused on the acute use of nitrate compounds as a means to deliver nitric oxide (NO) to improve pulmonary vasculature relaxation during an acute bout of exercise. In the figure below, pulmonary capillary wedge pressure (PCWP) was lower by 10 mmHg after administration of intra-venous nitrite, a precursor to nitric oxide.

A similar approach to reducing cardiac filling pressures during exercise is creation of an inter-atrial septostomy. In a recent study of 64 HFpEF patients, an inter-atrial septostomy was created by placing an Amplatzer like device with an 8 mm opening allowing for communication between left and right atria. (Hasenfuss et al., 2016) After 6 months, subjects and increased exercise tolerance as well as a slight reduction in exercise

PCWP (32 to 29 mmHg) suggesting relief of excessively high intra-cardiac pressures during exercise is a viable therapy for improving functional capacity and improving quality of life.



Acute administration of IV nitrite during exercise lowers pulmonary capillary wedge pressures during exercise. (Borlaug et al; JACC 2015)

Conclusion

HFpEF accounts for nearly half of new heart failure diagnoses. While rates of HFpEF have seemed to stabilize, the disease presents a number of diagnostic and therapeutic challenges. There remain no proven therapies for the syndrome with considerable controversy around the key pathophysiologic mechanisms responsible for limitations in exercise tolerance. Focus has shifted on ameliorating exercise induced symptoms but further work on understanding the pathologic stiffening and impairment in ventricular relaxation is necessary. Until then, treatment options are limited to exercise training, weight loss and treatment of concomitant co-morbid conditions.

References:

Bhatia, R.S., Tu, J.V., Lee, D.S., Austin, P.C., Fang, J., Haouzi, A., Gong, Y., and Liu, P.P. (2006). Outcome of heart failure with preserved ejection fraction in a population-based study. N Engl J Med *355*, 260-269.

Borlaug, B.A., and Kass, D.A. (2008). Ventricular-vascular interaction in heart failure. Heart failure clinics *4*, 23-36.

Bursi, F., Weston, S.A., Redfield, M.M., Jacobsen, S.J., Pakhomov, S., Nkomo, V.T., Meverden, R.A., and Roger, V.L. (2006). Systolic and diastolic heart failure in the community. JAMA *296*, 2209-2216.

Carrick-Ranson, G., Hastings, J.L., Bhella, P.S., Fujimoto, N., Shibata, S., Palmer, M.D., Boyd, K., Livingston, S., Dijk, E., and Levine, B.D. (2014). The effect of lifelong exercise dose on cardiovascular function during exercise. Journal of applied physiology *116*, 736-745.

Coutinho, T., Borlaug, B.A., Pellikka, P.A., Turner, S.T., and Kullo, I.J. (2013). Sex differences in arterial stiffness and ventricular-arterial interactions. J Am Coll Cardiol *61*, 96-103.

Edelmann, F., Wachter, R., Schmidt, A.G., Kraigher-Krainer, E., Colantonio, C., Kamke, W., Duvinage, A., Stahrenberg, R., Durstewitz, K., Loffler, M*., et al.* (2013). Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: the Aldo-DHF randomized controlled trial. JAMA *309*, 781-791.

Fonarow, G.C., Stough, W.G., Abraham, W.T., Albert, N.M., Gheorghiade, M., Greenberg, B.H., O'Connor, C.M., Sun, J.L., Yancy, C.W., and Young, J.B. (2007). Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. J Am Coll Cardiol *50*, 768-777.

Hasenfuss, G., Hayward, C., Burkhoff, D., Silvestry, F.E., McKenzie, S., Gustafsson, F., Malek, F., Van der Heyden, J., Lang, I., Petrie, M.C*., et al.* (2016). A transcatheter intracardiac shunt device for heart failure with preserved ejection fraction (REDUCE LAP-HF): a multicentre, open-label, single-arm, phase 1 trial. Lancet *387*, 1298-1304.

Kass, D.A., Kitzman, D.W., and Alvarez, G.E. (2010). The restoration of chronotropic competence in heart failure patients with normal ejection fraction (RESET) study: rationale and design. J Card Fail *16*, 17-24.

Kawaguchi, M., Hay, I., Fetics, B., and Kass, D.A. (2003). Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction: implications for systolic and diastolic reserve limitations. Circulation *107*, 714-720.

Kelly, R.P., Ting, C.T., Yang, T.M., Liu, C.P., Maughan, W.L., Chang, M.S., and Kass, D.A. (1992). Effective arterial elastance as index of arterial vascular load in humans. Circulation *86*, 513-521.

Kitzman, D.W., Herrington, D.M., Brubaker, P.H., Moore, J.B., Eggebeen, J., and Haykowsky, M.J. (2013). Carotid arterial stiffness and its relationship to exercise intolerance in older patients with heart failure and preserved ejection fraction. Hypertension *61*, 112-119.

Lauer, M.S., Anderson, K.M., Kannel, W.B., and Levy, D. (1991). The impact of obesity on left ventricular mass and geometry. The Framingham Heart Study. Jama *266*, 231-236.
Mogelvang, R., Sogaard, P., Pedersen, S.A., Olsen, N.T., Schnohr, P., and Jensen, J.S. (2009). Tissue Doppler echocardiography in persons with hypertension, diabetes, or ischaemic heart disease: the Copenhagen City Heart Study. European heart journal *30*, 731-739.
Mohammed, S.F., Hussain, S., Mirzoyev, S.A., Edwards, W.D., Maleszewski, J.J., and Redfield, M.M. (2015). Coronary microvascular rarefaction and myocardial fibrosis in heart failure with preserved ejection fraction. Circulation *131*, 550-559.
Owan, T.E., Hodge, D.O., Herges, R.M., Jacobsen, S.J., Roger, V.L., and Redfield, M.M. (2006). Trends in prevalence and outcome of heart failure with preserved ejection fraction. The New England journal of medicine *355*, 251-259.
Pandey, A., Parashar, A., Kumbhani, D.J., Agarwal, S., Garg, J., Kitzman, D., Levine, B.D., Drazner, M., and Berry, J.D. (2015). Exercise training in patients with heart failure and preserved ejection fraction: meta-analysis of randomized control trials. Circ Heart Fail *8*, 33-40.
Pitt, B., Pfeffer, M.A., Assmann, S.F., Boineau, R., Anand, I.S., Claggett, B., Clausell, N., Desai, A.S., Diaz, R., Fleg, J.L.*, et al.* (2014). Spironolactone for heart failure with preserved ejection fraction. N Engl J Med *370*, 1383-1392.
Popovic, Z.B., Prasad, A., Garcia, M.J., Arbab-Zadeh, A., Borowski, A., Dijk, E., Greenberg, N.L., Levine, B.D., and Thomas, J.D. (2006). Relationship among diastolic intraventricular pressure gradients, relaxation, and preload: impact of age and fitness. American journal of physiology Heart and circulatory physiology *290*, H1454-1459.
Prasad, A., Hastings, J.L., Shibata, S., Popovic, Z.B., Arbab-Zadeh, A., Bhella, P.S., Okazaki, K., Fu, Q., Berk, M., Palmer, D.*, et al.* (2010). Characterization of static and dynamic left ventricular diastolic function in patients with heart failure with a preserved ejection fraction. Circulation Heart failure *3*, 617-626.
Redfield, M.M., Chen, H.H., Borlaug, B.A., Semigran, M.J., Lee, K.L., Lewis, G., LeWinter, M.M., Rouleau, J.L., Bull, D.A., Mann, D.L.*, et al.* (2013). Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial. JAMA *309*, 1268-1277.
Roger, V.L., Go, A.S., Lloyd-Jones, D.M., Adams, R.J., Berry, J.D., Brown, T.M., Carnethon, M.R., Dai, S., de Simone, G., Ford, E.S.*, et al.* (2011). Heart disease and stroke statistics--2011 update: a report from the American Heart Association. Circulation *123*, e18-e209.
Russo, C., Jin, Z., Homma, S., Rundek, T., Elkind, M.S., Sacco, R.L., and Di Tullio, M.R. (2011). Effect of obesity and overweight on left ventricular diastolic function: a community-based study in an elderly cohort. Journal of the American College of Cardiology *57*, 1368-1374.
Schwartzenberg, S., Redfield, M.M., From, A.M., Sorajja, P., Nishimura, R.A., and Borlaug, B.A. (2012). Effects of vasodilation in heart failure with preserved or reduced ejection fraction implications of distinct pathophysiologies on response to therapy. Journal of the American College of Cardiology *59*, 442-451.
Tartiere-Kesri, L., Tartiere, J.M., Logeart, D., Beauvais, F., and Cohen Solal, A. (2012). Increased proximal arterial stiffness and cardiac response with moderate exercise in

patients with heart failure and preserved ejection fraction. Journal of the American College of Cardiology *59*, 455-461.
Zile, M.R., Baicu, C.F., Ikonomidis, J.S., Stroud, R.E., Nietert, P.J., Bradshaw, A.D., Slater, R., Palmer, B.M., Van Buren, P., Meyer, M.*, et al.* (2015). Myocardial stiffness in patients with heart failure and a preserved ejection fraction: contributions of collagen and titin. Circulation *131*, 1247-1259.
Zile, M.R., and Brutsaert, D.L. (2002). New concepts in diastolic dysfunction and diastolic heart failure: Part I: diagnosis, prognosis, and measurements of diastolic function. Circulation *105*, 1387-1393.