Cardiovascular Effects of 1 Year of Alagebrium and Endurance Exercise Training in Healthy Older Individuals

Summary: Lifelong exercise training maintains a youthful compliance of the left ventricle (LV), whereas a year of exercise training started later in life fails to reverse LV stiffening, possibly because of accumulation of irreversible advanced glycation end products. Alagebrium is a novel drug that breaks advanced glycation end products crosslinks and improves LV stiffness in aged animals. In this study, the authors prescribed alagebrium (200 mg daily) or placebo combined with aerobic exercise training or contact control in healthy, sedentary older individuals for 1 year. The authors evaluated overall cardiac function by the use of several modalities, including invasive pressure–volume measurements, exercise testing, and cardiac MRI before and after the training. To the authors’ knowledge, this is the first study to evaluate the effects of alagebrium and exercise training in healthy aged humans. After intervention, exercise training significantly increased exercise capacity, LV mass, and LV end-diastolic volume. Conversely, alagebrium had little effect on exercise capacity or LV geometry. However, alagebrium showed a modest improvement in LV stiffness compared with placebo. This favorable effect of alagebrium on LV stiffness was most prominent in individuals with combined alagebrium and exercise training.

Conclusions: Alagebrium had no effect on hemodynamics, LV geometry, or exercise capacity in healthy, previously sedentary seniors. However, it did show a modestly favorable effect on age-associated LV stiffening.

Prognostic Value of Exercise Testing During Heart Transplant Evaluation in Children

Summary: Maximum oxygen consumption (peak VO2) and efficiency of ventilation (VE) during exercise (VE/VCO2 slope) are known to stratify adults in heart failure for 1-year survival. On the basis of adult data, a recent American Heart Association scientific statement suggested that peak VO2<50% predicted for age and sex should be considered substantial impairment in exercise performance in children with heart disease and therefore a class I indication for heart transplant listing. This single-center study examined the association of peak VO2<50% predicted with risk of death or deterioration in 50 children evaluated for heart transplant during 2002 to 2011 (32 biventricular circulation, 18 palliated single ventricle). Overall, 24 children reached the composite end point (death, urgent transplant, or initiation of mechanical support). Although children with peak VO2<50% predicted and those with peak VO2≥50% predicted were equally likely to be listed, children with peak VO2<50% predicted were at 4.7-fold risk of death or deterioration on follow-up compared with those with peak VO2≥50% predicted among those with a biventricular circulation. VE/VCO2 slope ≥34 during exercise testing was also associated with poor outcome in children with biventricular circulation. Exercise testing was unable to risk-stratify children with a palliated single ventricle.

Conclusions: Exercise testing during HT evaluation in children with biventricular circulation identified those at higher risk of death or deterioration in this small study. Larger studies are needed to assess the role of exercise testing during HT evaluation in children with a palliated single ventricle.

Effects of Exercise on Left Ventricular Systolic and Diastolic Properties in Patients With Heart Failure and a Preserved Ejection Fraction Versus Heart Failure and a Reduced Ejection Fraction

Summary: The purpose of the current study was to define exercise-induced changes in indices of left ventricular systolic and diastolic properties in patients with chronic heart failure (HF), and in particular to compare these changes in patients with HF and a reduced ejection fraction (HFrEF) versus HF and a preserved EF (HFpEF). These results provided new and unique insights into understanding of exercise-induced changes in systolic and diastolic properties. For example, although the increase in cardiac output was blunted in both patients with HFrEF and HFpEF, the mechanisms underlying this limitation were significantly different. In HFrEF, systolic properties fell during exercise, but the recruitment of Frank–Starling mechanisms allowed some increase in stroke volume. By contrast, in patients with HFpEF, there was no recruitment of Frank–Starling mechanisms, but a small increase in left ventricular systolic properties allowed an increase in stroke volume. Left ventricular diastolic pressures rose during exercise, but the recruitment of Frank–Starling mechanisms was minimal. These data support the conclusion that although a number of mechanisms limit exercise in HFrEF, 1 dominant mechanism is the abnormalities in diastolic function. By contrast, although a number of mechanisms limit exercise in HFpEF, 1 dominant mechanism is the abnormalities in systolic function. These data may serve to underscore the differences in pathophysiology of the clinical syndrome of HFrEF versus HFpEF.

Conclusions: Although exercise limitations were similar between HF and a reduced EF and HF and a preserved EF, there were significant
differences in exercise-induced changes in LV systolic and diastolic properties. These differences likely reflect the different pathophysiologicals of these clinical syndromes of HF.

Validation of a Cardiopulmonary Exercise Test Score in Heart Failure

Summary: The cardiopulmonary exercise test (CPX) has been widely used in recent years to stratify risk in patients with heart failure. However, the optimal method of applying CPX responses remains a topic of debate. The authors recently developed a multivariate CPX score that integrated the additive prognostic information from 5 CPX responses. The purpose of this study was to validate the score in a larger, independent sample of patients with heart failure. The authors studied 2625 adults with heart failure who underwent CPX and were followed for a mean of 29±30 months. The score was derived by weighting the age-adjusted prognostic power of 5 CPX variables using a summary of point-based risk scores. The VE/VO2 slope (≥234) was attributed a relative weight of 7, with weighted scores for abnormal heart rate recovery at 1 minute, oxygen uptake efficiency slope, resting end-tidal CO2 pressure, and peak VO2 having scores of 5, 3, 3, and 2, respectively. A summed score of >15 was associated with a 4% lower risk of the primary composite end point of death, HTx, or V AD requirements. V AD-free or HTx-free survival of patients with peak VO2 10 to 14 mL/min per kg was identical to post-HTx survival. When patients with peak VO2 10 to 14 mL/min per kg were dichotomized by a cutoff value of BNP of 506 pg/mL, survival of those with BNP<506 pg/mL was equivalent to post-HTx survival, whereas those with BNP>506 showed worse VAD-free or HTx-free survival compared with post-HTx survival. Therefore, patients with peak VO2 10 to 14 mL/min per kg and low BNP levels have a VAD-free or HTx-free survival similar to post-HTx survival in heart recipients, whereas increased levels of BNP indicate worse outcome in this group of patients.

Conclusions: These results validate the application of a simple, integrated multivariable score based on readily available CPX responses.

Value of Peak Exercise Oxygen Consumption Combined With B-Type Natriuretic Peptide Levels for Optimal Timing of Cardiac Transplantation

Summary: Peak exercise oxygen consumption (VO2) obtained during cardiopulmonary exercise testing has been widely used to select candidates for heart transplantation (HTx). However, the prognosis of patients with moderately decreased peak VO2 (10–14 mL/min per kg) has not been fully elucidated. In the present study, the authors compared the survival without ventricular assist device (VAD) or HTx of 424 patients undergoing cardiopulmonary exercise testing who were classified based on their peak VO2 values with posttransplant survival of 743 HTx recipients. Furthermore, the impact of B-type natriuretic peptide (BNP) for the assessment of prognosis in patients undergoing cardiopulmonary exercise testing was analyzed. Multivariable analysis revealed that high BNP and low peak VO2 were independently associated with death, HTx, or VAD requirements. VAD-free or HTx-free survival of patients with peak VO2 10 to 14 mL/min per kg was identical to post-HTx survival. When patients with peak VO2 10 to 14 mL/min per kg were dichotomized by a cutoff value of BNP of 506 pg/mL, survival of those with BNP<506 pg/mL was equivalent to post-HTx survival, whereas those with BNP>506 showed worse VAD-free or HTx-free survival compared with post-HTx survival.

Conclusions: The cardiopulmonary exercise test (CPX) has been widely used in recent years to stratify risk in patients with heart failure. However, the optimal method of applying CPX responses remains a topic of debate. The authors recently developed a multivariate CPX score that integrated the additive prognostic information from 5 CPX variables using a summary of point-based risk scores. The VE/VO2 slope (≥234) was attributed a relative weight of 7, with weighted scores for abnormal heart rate recovery at 1 minute, oxygen uptake efficiency slope, resting end-tidal CO2 pressure, and peak VO2 having scores of 5, 3, 3, and 2, respectively. A summed score of >15 was associated with a 4% lower risk of the primary composite end point of death, HTx, or VAD requirements. VAD-free or HTx-free survival of patients with peak VO2 10 to 14 mL/min per kg was identical to post-HTx survival. When patients with peak VO2 10 to 14 mL/min per kg were dichotomized by a cutoff value of BNP of 506 pg/mL, survival of those with BNP<506 pg/mL was equivalent to post-HTx survival, whereas those with BNP>506 showed worse VAD-free or HTx-free survival compared with post-HTx survival. Therefore, patients with peak VO2 10 to 14 mL/min per kg and low BNP levels have a VAD-free or HTx-free survival similar to post-HTx survival in heart recipients, whereas increased levels of BNP indicate worse outcome in this group of patients.

Expression of the Irisin Precursor FNDC5 in Skeletal Muscle Correlates With Aerobic Exercise Performance in Patients With Heart Failure

Summary: Exercise intolerance is a common symptom among heart failure (HF) patients with profound clinical ramifications. Both central (cardiac output, alveolar perfusion) and peripheral (skeletal muscle, capillary perfusion) mechanisms have been implicated. Moderate-intensity aerobic exercise training typically improves functional capacity with little or no impact on central cardiac parameters, highlighting the importance of peripheral physiology on HF management. Nonetheless, pertinent HF effects on skeletal muscle remain poorly defined. Aerobic exercise training has been demonstrated to induce a more oxidative skeletal muscle phenotype, characterized by increased expression of the transcriptional coactivator peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) and mitochondrial growth. Recent animal studies have also demonstrated that irisin, a newly described myokine, is induced by exercise through the action of PGC-1α to stimulate changes in adipose tissue that mediate improvements in systemic metabolism. The authors hypothesized that expression of PGC-1α and FNDC5 (the genetic precursor of irisin) relates to aerobic performance in human HF patients. The authors measured aerobic capacity (cardiopulmonary exercise testing indices peak oxygen consumption and ventilatory efficiency slope) in 24 patients with systolic HF (left ventricular ejection fraction ≤40%). The authors assessed PGC-1α and FNDC5 from skeletal muscle biopsies. The authors demonstrated that PGC-1α and FNDC5 gene expressions are greater in the patients with the greater functional capacity (peak oxygen consumption >14 mL·kg⁻¹·min⁻¹, ventilatory efficiency slope <34).

Conclusions: This is the first study to show that FNDC5 expression relates to functional capacity in a human HF population. Lower FNDC5 expression may underlie reduced aerobic performance in HF patients.

Modest Increase in Peak VO2 Is Related to Better Clinical Outcomes in Chronic Heart Failure Patients: Results From Heart Failure and a Controlled Trial to Investigate Outcomes of Exercise Training

Summary: In this substudy of the landmark clinical trial entitled Heart Failure and a Controlled Trial to Investigate Outcomes of Exercise Training, Swank et al report that small increments in peak oxygen uptake (VO2) are associated with clinical outcome benefits in patients with heart failure. Specifically, every 6% increase in peak VO2, adjusted for other significant predictors, was associated with a 5% lower risk of the primary composite end point of all-cause mortality and morbidity; a 4% lower risk of the secondary end point of time to cardiovascular mortality or cardiovascular hospitalization; an 8% lower risk of cardiovascular mortality or heart failure hospitalization; and a 7% lower all-cause mortality. Although it was difficult to attribute the results to exercise training per se, the fact that a relatively small increase in fitness improved clinical outcomes supports the concept that improving VO2 may be an important target of therapy, however it is achieved. The study also has implications for the often-asked question not only in rehabilitation studies but also for drug and exercise testing who are in a euvolemic state and on optimized medical therapy.

Conclusions: Patients with peak VO2 10 to 14 mL/min per kg and low BNP levels have a VAD-free or HTx-free survival similar to post-HTx survival in heart recipients, whereas high BNP levels indicate worse outcome in this group of patients.
device interventions: What constitutes a significant change in peak VO2? The information provided from this study that an incremental change in peak VO2 as low as 6% has morbidity and mortality benefit provides a potential benchmark for clinicians and trialists.

Conclusions: Among patients with chronic systolic heart failure, a modest increase in peak VO2 over 3 months was associated with a more favorable outcome. Monitoring the change in peak VO2 for such patients may have benefit in assessing prognosis.

Effect of β-Blocker Cessation on Chronotropic Incompetence and Exercise Tolerance in Patients With Advanced Heart Failure

Summary: This is the first study to address the effects of β-blocker cessation on both chronotropic incompetence and exercise tolerance in patients with advanced heart failure. The authors demonstrate that short-term absence of β-blockers does not affect chronotropic incompetence or heart rate response to norepinephrine in these patients. Therefore, the authors further support the hypothesis that impaired chronotropic response during exercise is an intrinsic component of advanced heart failure that cannot be overcome by acute withdrawal of β-blockers. It is common that patients with advanced heart failure present to their clinician with complaints of exercise intolerance. The clinician must decide whether discontinuing β-blocker therapy offers an improvement in exercise tolerance and, therefore, perhaps quality of life. The clinician often relies on prior experience and anecdotal data to guide this decision. However, discontinuation of β-blockers is problematic given the substantial survival benefit derived from these agents in advanced heart failure. These data may inform the decision as to whether to continue β-blockers in patients with advanced heart failure and chronotropic incompetence for whom rate-responsive therapy is being considered.

Conclusions: Acute β-blocker cessation does not normalize the chronotropic response to exercise in patients with advanced HF and chronotropic incompetence.

Exercise Hemodynamics in Patients With and Without Diastolic Dysfunction and Preserved Ejection Fraction After Myocardial Infarction

Summary: Several studies have demonstrated that normal left ventricular (LV) filling pattern is only seen in one third of patients in the acute phase of myocardial infarction. When LV filling is severely abnormal, survival is poor and the risk of developing heart failure is high. However, most patients do not present with severely abnormal LV filling pattern, and patients with less severe diastolic dysfunction often display only minor evidence of myocardial damage, with preserved LV systolic function. The cause and hemodynamic consequences of abnormal LV filling in these patients are poorly understood, and abnormalities may only be apparent during increased circulatory demands, such as exercise. The present study demonstrates that in patients with a recent myocardial infarction, with preserved LV ejection fraction and diastolic dysfunction on Doppler echocardiography, filling pressures with exercise increase substantially and significantly more than in comparable myocardial infarction patients without baseline diastolic dysfunction or in healthy controls. Thus, abnormal LV filling on Doppler echocardiography at rest identifies a group of patients who are only able to obtain a sufficient increase in cardiac output during exercise at the expense of elevated filling pressures. Abnormal LV filling is an early morphological expression that may identify patients at increased risk of developing heart failure.

Conclusions: In post-MI patients with preserved ejection fraction and left ventricular DD, cardiac output with exercise is maintained at the expense of substantially increased filling pressure. DD and loss of diastolic reserve may promote progression from stage B to stage C heart failure after MI.

Phosphoinositide 3-Kinase p110α Is a Master Regulator of Exercise-Induced Cardioprotection and PI3K Gene Therapy Rescues Cardiac Dysfunction

Summary: The beneficial effects of regular physical activity on cardiovascular health are well established. However, the key molecular mechanisms underlying the cardioprotective effects of exercise are not well defined. Identification of critical pathways that are activated by exercise may lead to novel and viable therapeutic intervention strategies. Although activation of phosphoinositide 3-kinase (PI3K) p110α was previously shown to be critical for physiological heart growth, its contribution and importance in exercise-induced cardiac protection were unknown. Here, the authors demonstrate that PI3K(p110α) is essential for swim-exercise-induced cardiac protection. Exercise was unable to mediate any protection when PI3K(p110α) activity was reduced in hearts of mice subjected to pressure overload. Furthermore, by using a gene therapy approach to increase PI3K in hearts of mice with preexisting cardiac dysfunction, the authors showed improved heart function over time. Because the tumorigenic properties of PI3K(p110α) are known in other cell types, the authors achieved muscle-specific delivery with a recombinant adeno-associated viral pseudotype vector that selectively transduces cardiac muscle. Significant developments in vector design and manufacturing, together with the recent entry of an adeno-associated virus–based intervention in a phase 2 trial in heart failure patients, highlight the potential of establishing adeno-associated virus–based delivery of PI3K(p110α) as a potential therapeutic gene delivery strategy in the clinic.

Conclusions: PI3K(p110α) is essential for exercise-induced cardioprotection and delivery of caPI3K vector can improve function of the failing heart.

Efficacy and Cost of an Exercise Program for Functionally Impaired Older Patients With Heart Failure: A Randomized Controlled Trial

Summary: A large body of evidence supports a role for exercise training in improving muscle function, quality of life, and hospitalization rates in patients with heart failure, but few studies have attempted to translate this evidence into programs that can be used by very old patients with heart failure. Results from this randomized controlled trial show a lack of benefit from an exercise program designed specifically for use in very old patients, functionally impaired patients with heart failure. Six-minute walk distance, quality of life, daily activity, functional ability, psychological state, and carer strain showed no difference between the intervention and control groups at 8 or 24 weeks. Only sit-to-stand time showed improvement with the exercise program compared with the control group. These results suggest that further work is required to design an effective exercise program for use by the oldest patients with heart failure and that programs used in younger patients cannot be assumed to be effective in very old patients.

Conclusions: This exercise intervention did not improve exercise capacity or quality of life in older patients with heart failure and was not cost saving to the National Health Service.

The Safety of Cardiopulmonary Exercise Testing in a Population With High-Risk Cardiovascular Diseases

Summary: Cardiopulmonary exercise testing (CPX) with measurement of peak oxygen uptake (VO2) is the most accurate test for
quantification of functional impairment resulting from cardiovascular disease. CPX has primarily been applied in patients with congestive heart failure to help select candidates for heart transplantation. There are other cardiovascular disorders (aortic stenosis, hypertrophic cardiomyopathy, pulmonary hypertension, and congenital heart disease) for which accurate assessment of functional capacity could serve as a useful aid in the clinical management of these patients. However, CPX has not been widely applied in these patient subsets, in part because of limited availability of safety data. This study investigated safety of CPX in 4250 patients with a wide variety of underlying high-risk cardiovascular diseases who underwent a total of 5060 tests. CPX was found to be reasonably safe in this study cohort, with an adverse event rate of 0.16% and no fatal events. This research may lead to further clinical application of CPX in these patient subsets.

Conclusions: CPX is generally a safe procedure, even in a population with underlying high-risk cardiovascular diagnoses.12

Exercise Training Attenuates MuRF-1 Expression in the Skeletal Muscle of Patients With Chronic Heart Failure Independent of Age: The Randomized Leipzig Exercise Intervention in Chronic Heart Failure and Aging Catabolism Study

Summary: Exercise intolerance in chronic heart failure (CHF) is influenced not only by the degree of left ventricular systolic dysfunction but also by peripheral skeletal muscle abnormalities, which commonly develop in advanced CHF and may progress to cardiac cachexia. Despite the clinical importance of muscle wasting in CHF, the molecular mechanisms are still largely unknown, and no specific anticatabolic treatment is currently available. In the Leipzig Exercise Intervention in Chronic Heart Failure and Aging (LEICA) study, skeletal muscle biopsies were obtained from the quadriceps muscles in younger and older CHF patients and in age-matched healthy subjects to analyze whether an important signaling system for intracellular protein degradation called the ubiquitin-proteasome system was activated in heart failure and whether activation was higher with older age. The authors found that one of the key enzymes that marks structural proteins for protein degradation (MuRF-1) was significantly elevated in muscle biopsies from CHF patients in both age groups. Four comprehensive resting and exercise stress echocardiography to evaluate the presence of pulmonary hypertension (PHT). The results showed that 55% of asymptomatic patients may develop exercise PHT. Patients with exercise PHT had significantly lower cardiac event-free survival and a markedly higher rate of death than those without exercise PHT. In addition, exercise PHT was associated with poorer outcome independently of demographic and resting echocardiographic data and exercise-induced changes in mean transaortic pressure gradient. Beyond both resting aortic stenosis severity and systolic pulmonary arterial pressure, the assessment of the presence of exercise PHT provided important incremental predictive value. Even in patients with markedly elevated aortic jet velocity, those with exercise PHT depicted a higher risk of reduced cardiac event-free survival. These results strongly support the use of exercise stress echocardiography in the management of asymptomatic severe aortic stenosis. Early elective aortic valve surgery to prevent irreversible left ventricular myocardial damage, diastolic dysfunction, and symptoms could be advised in patients developing exercise PHT. In contrast, asymptomatic patients with no exercise PHT may be conservatively followed up.

Conclusions: In asymptomatic patients with severe aortic stenosis, the main determinants of Ex-PHT are male sex, resting systolic pulmonary arterial pressure, and exercise parameters of diastolic burden. Moreover, Ex-PHT is associated with a 2-fold increased risk of cardiac events. These results strongly support the use of exercise stress echocardiography in asymptomatic aortic stenosis.14

Long-Term Effects of Sildenafil in a Rat Model of Chronic Mitral Regurgitation: Benefits of Ventricular Remodeling and Exercise Capacity

Summary: Mitral regurgitation (MR) induces chronic left ventricular volume overload and leads to left ventricular contractile dysfunction, heart failure, and, finally, death. Although surgical correction of MR, the only definitive cure, carries reasonably low mortality and morbidity risks, medical therapeutics have a role in many clinical situations such as in a patient population with greater surgical risk. However, there is currently no recommended pharmacological therapy for chronic MR. Despite previous efforts, medical therapies for chronic MR have produced disappointing and conflicting results. Since the early 2000s, sildenafil, part of a class of selective inhibitors of phosphodiesterase type 5, has been under intense study in various areas. Multiple lines of preclinical and clinical evidence support a therapeutic role for phosphodiesterase type 5 inhibition with sildenafil in the management of heart failure. Accordingly, the authors hypothesized that sildenafil may have a beneficial effect in chronic MR. The major findings of the present study are that sildenafil prevented left ventricular remodeling and exercise intolerance caused by chronic experimental MR. To the authors’ knowledge, this is the first study that shows that sildenafil is efficacious in the presence of MR. Additionally, the authors proposed potential mechanisms related to the effect of sildenafil: inhibition of inflammation and apoptosis. With consideration of the beneficial effects of sildenafil in MR rats, the authors can expect a therapeutic potential for sildenafil in patients with MR. Future clinical studies are needed.

Conclusions: Sildenafil significantly attenuates LV remodeling and prevents exercise intolerance in a rat model of chronic MR. This benefit may be associated with the antiapoptotic, anti-inflammatory effects of sildenafil.15

Comprehensive Use of Cardiopulmonary Exercise Testing Identifies Adults With Congenital Heart Disease at Increased Mortality Risk in the Medium Term

Summary: Cardiopulmonary exercise testing (CPX) has emerged as an important tool for risk stratification in adults with congenital heart disease. However, it remains uncertain how best to apply CPX parameters in clinical practice. Relating a CPX result to prognosis may be difficult for clinicians because previous studies based on
conventional statistical analyses provide relative risk estimates rather than actual projected risk. Moreover, it is unclear how CPX parameters should be combined to best obtain prognostic information. The authors assessed the relation between CPX parameters and midterm survival in 1375 adult congenital heart disease patients at a tertiary center over a 10-year period (median follow-up, 5.8 years). Estimated 5-year survival rates as a function of peak oxygen consumption, heart rate reserve, and ventilation per unit of carbon dioxide production (VE/VCO2 slope) were calculated. The combination of peak oxygen consumption and heart rate reserve provided the greatest predictive information after adjustment for clinical parameters such as negative chronotropic agents, age, and presence of cyanosis. However, the incremental value of these exercise parameters was reduced in patients with peak respiratory exchange ratio <1.0. CPX provides strong prognostic information in adult patients with congenital heart disease. Prognostication should be approached differently, depending on the presence of cyanosis, use of rate-lowering medications, and achieved level of exercise. The authors provide 5-year survival prospects based on CPX parameters in this growing population.18

Conclusions: Cardiopulmonary exercise testing provides strong prognostic information in adult patients with congenital heart disease. Prognostication should be approached differently, depending on the presence of cyanosis, use of rate-lowering medications, and achieved level of exercise. The authors provide 5-year survival prospects based on cardiopulmonary exercise testing parameters in this growing population.18

Poorer Right Ventricular Systolic Function and Exercise Capacity in Women After Repair of Tetralogy of Fallot: A Sex Comparison of Standard Deviation Scores Based on Sex-Specific Reference Values in Healthy Control Subjects

Summary: The specific findings in this study were relevant sex differences of cardiopulmonary function in repaired tetralogy of Fallot (r-ToF), independently of type and result of repair. The young study cohort, with almost identical preoperative and postoperative characteristics for both sexes, showed significant poorer results for girls, relating to age- and sex-matched healthy references, compared with boys. This suggests that female patients with r-ToF are at greater risk for cardiac failure, which seems to be supported by functional data of adults; however, data on sex issues in r-ToF are sparse. These findings may initiate reconsideration of current guidelines in r-ToF, concerning recommendations for pulmonary valve replacement, as well as in other congenital heart defects for which guidelines do not yet systemically reflect sex aspects, in addition to encouraging basic research on role of sex in congenital heart disease.

Conclusions: Relative to their respective sex-specific healthy control subjects, derived standard deviation scores in repaired tetralogy of Fallot suggest that women perform poorer than men in terms of right ventricular systolic function as tested by cardiac magnetic resonance and exercise capacity. This effect cannot be explained by selection bias. Further outcome data are required from longitudinal cohort studies.17

Prognostic Significance of Exercise-induced Right Ventricular Dysfunction in Asymptomatic Degenerative Mitral Regurgitation

Summary: Exercise echocardiography has a role in the management of asymptomatic mitral regurgitation (MR), where it may be useful in the unmasking of occult symptoms, left ventricular contractile reserve, worsening MR with stress, and identification exercise-induced pulmonary hypertension (exPH). The role of exPH in decision making regarding surgical timing for asymptomatic chronic MR is controversial, partly because of variability in responses. The authors reasoned that the exPH response could not be interpreted without knowledge of right ventricular (RV) function. The authors aimed to explore the role of RV measures at rest and during exercise to predict prognosis (survival free of mitral surgery) in 196 asymptomatic patients with moderate to severe MR and preserved left ventricular function. Exercise-induced RV dysfunction, measured by exercise TAPSE, as well as exPH and left ventricular and RV strain at rest were independent predictors of survival free of mitral surgery. Moreover, the authors showed the incremental predictive value of exercise RV dysfunction for prognosis over a model based on clinical data and exPH. Early selection for surgery may improve prognosis in selected patients with asymptomatic MR, and the results of this study suggest that exercise RV dysfunction should be considered as an additional risk marker in these patients.

Conclusions: Exercise-induced RV dysfunction provides important incremental prognostic value in the management of asymptomatic mitral regurgitation.18

Cardiac Magnetic Resonance Imaging: A New Gold Standard for Ventricular Volume Quantification During High-Intensity Exercise

Summary: Exercise intolerance defines many cardiac disease processes, yet cardiac imaging is most frequently performed at rest. In heart failure patients, abnormalities in cardiac function may be subtle or absent at rest but apparent under physiological stress. However, the increased diagnostic potential of exercise imaging may be realized only if functional measures can be performed and remain robust throughout exercise. In this article, the authors describe a novel MRI technique, real-time ungated cardiac MRI (RT-ungated CMR), for measuring biventricular volumes during high-intensity exercise. Compared with an invasive reference technique, the authors demonstrate that RT-ungated CMR is feasible, reproducible, and accurate in a wide range of subjects, from patients with markedly reduced cardiac reserve to athletes with supernormal outputs during exercise. RT-ungated CMR represents a new gold standard in imaging during exercise that enables a comprehensive assessment of biventricular filling and emptying at the time when cardiac output demand starts to exceed capacity. Therefore, the technique provides unique insight into cardiac constraints in both health and disease. This may be of particular value for the right ventricle, which is difficult to assess with other imaging modalities but is an important determinant of prognosis in conditions affecting the pulmonary vasculature, including pulmonary hypertension secondary to left heart failure. RT-ungated CMR is an ideal tool for selecting heart failure patients who may derive the greatest benefit from therapies targeting the right ventricle and pulmonary circulation. The accuracy of RT-ungated CMR may also facilitate the diagnosis of evolving or subclinical cardiomyopathies secondary to diabetes mellitus, hypertension, or sarcoidosis.

Conclusions: When RT-ungated CMR is combined with post hoc analysis incorporating compensation for respiratory motion, highly reproducible and accurate biventricular volumes can be measured during maximal exercise.19

Exercise Response in Hypertrophic Cardiomyopathy: Blunted Left Ventricular Deformational and Twisting Reserve With Altered Systolic-Diastolic Coupling

Summary: The authors investigated the adaptation of left ventricular (LV) strains and twist-untwist mechanics in hypertrophic cardiomyopathy (HCM) patients, who typically show exercise-induced symptoms. At rest, HCM patients showed lower longitudinal strain than control subjects, and this was compensated for by higher circumferential strain and twist. During exercise, however, HCM patients exhibited a severely limited adaptability of all strain components with no LV twisting reserve, reduced and delayed untwist
mechanics, and reduced systolic-diastolic coupling efficiency. Exercise echocardiography with evaluation of LV twisting and deformational reserve might be a useful clinical tool in other cardiac pathologies, particularly in differentiating physiological and pathological hypertrophy. As opposed to pathological hypertrophy, the athlete’s heart would be expected to have an increased twisting and deformational reserve. However, this must be confirmed in further comparative studies.

Conclusions: HCM patients had severely limited strain adaptability and no LV twisting reserve at exercise. They had reduced and delayed UTR with reduced systolic-diastolic coupling efficiency by twist-twist mechanics.20

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