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PERCUTANEOUS AND MINIMALLY INVASIVE THERAPIES FOR THE MANAGEMENT OF STRUCTURAL HEART DISEASE

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The Structural Heart Disease (SHD) Program at Intermountain Medical Center is actively investigating innovative and minimally invasive methods of treating SHD. SHD broadly refers to congenital and noncoronary disease, such as septal defects, valvular heart disease or hypertrophic cardiomyopathy.

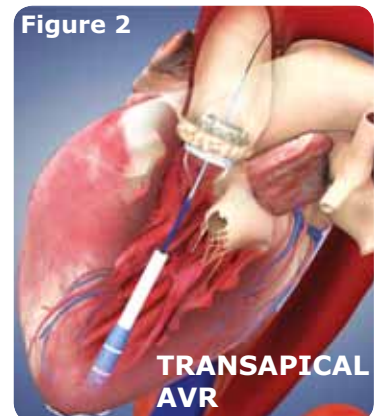
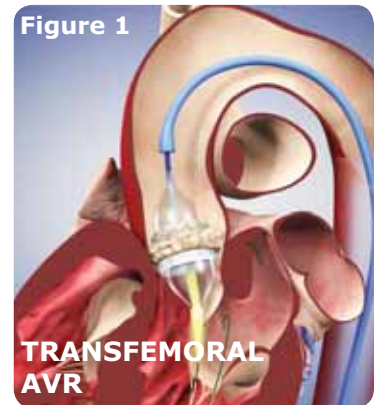
SHD care demands a multidisciplinary approach. Our program brings together experts in the fields of interventional cardiology, cardiac surgery, and cardiac imaging, including transesophageal and intracardiac echocardiography, cardiac CT and cardiac MRI. A hybrid cardiac cath lab/operating room has been built at our center to facilitate the care of patients and allow our multidisciplinary team to work in the same clinical space.

SHD program staff (physicians, surgeons, nurses and research coordinators) have built upon a long history of excellence in cardiovascular medicine established at LDS Hospital and subsequently transferred to Intermountain Medical Center. Our goal is to offer cutting-edge technologies in a setting that demands excellence and data-driven patient care. Here, we have summarized our current research trials and ongoing efforts in this relatively new field.

PERCUTANEOUS AORTIC VALVE REPLACEMENT – THE PARTNER TRIAL

Early observations predict that the PARTNER trial will long be remembered as the landmark trial launching a new era of percutaneous valve therapies. This trial randomized high-risk patients with critical aortic stenosis to either a surgical or a nonsurgical arm. The nonsurgical arm included percutaneous implantation via either a transfemoral or a transapical fashion (Figures 1 and 2 above).

Two percutaneous aortic valves are commercially available in Europe at this time: the Sapien Valve (Edwards Lifesciences, Irvine, CA) and the CoreValve® system (Medtronic,



The Sapien Valve. Images courtesy of Edwards Lifesciences, Irvine, CA.

Inc., Minneapolis, MN). With over 4000 commercial implants of each valve, adoption has exceeded expectations. Our own experience in the PARTNER trial was also successful with tremendous results in a cohort of high-risk aortic stenosis patients.

The PARTNER trial was initiated at our center in 2009 and completed enrollment in August. Our center is now participating in the FDA-approved, nonrandomized, continued access PARTNER registry with similar enrollment criteria outlined below.¹

PERCUTANEOUS AORTIC VALVE REPLACEMENT

The Partner Registry

KEY INCLUSION CRITERIA

ALL COHORTS

- Severe calcific aortic stenosis with echo derived valve area of $<0.8 \text{ cm}^2$ (EOA index $<0.5 \text{ cm}^2$) or mean gradient $>40 \text{ mmHg}$ or jet velocity $>4.0 \text{ m/s}$
- NYHA functional class II or greater

COHORT A

Receives transcatheter AVR (apical or femoral)

- Society of Thoracic Surgeons (STS) risk score of >10 or predicted operative mortality of 15% (Online STS risk calculator: www.sts.org/sections/stsnationaldatabase/riskcalculator/)

COHORT B

Receives transcatheter AVR (apical or femoral)

- Risk of death or serious irreversible morbidity must exceed 50% as assessed by STS risk score or by a cardiologist and two surgeons

KEY EXCLUSION CRITERIA

- Bicuspid or non-calcified aortic valve
- Severe LV dysfunction (LVEF $<20\%$)
- Any cardiac procedure within 30 days or within 6 months for drug eluting stent
- Severe AR or MR ($>3+$) or prosthetic valve (any location)
- Serum Cr >3.0 or dialysis dependent
- CVA or TIA within 6 months
- Life expectancy <12 months

PERCUTANEOUS MITRAL VALVE REPAIR

Intermountain Medical Center participated in the pivotal EVEREST II trial of percutaneous mitral valve repair using the MitraClip® (Evalve, Inc., Menlo Park, CA). See Figures 3 and 4. EVEREST II is currently in a follow-up phase without ongoing enrollment. However, a continued access registry called REALISM has been approved by the FDA, allowing us to

continue offering percutaneous mitral repair at our center. The mitral valve can also be repaired through a mini-thoracotomy with or without robotic assistance.

Early results from the Everest I feasibility trial, and certain data from non-randomized roll-in patients from EVEREST II trial, were recently published in the Journal of the American College of Cardiology.² Patients demonstrated a durable percutaneous valve repair beyond 36 months with few complications. A broad spectrum of patients, ages 47-91, with both functional and degenerative mitral regurgitation have been successfully treated by our program.



Figure 3



Figure 4

The MitraClip Device. Images courtesy of Evalve, Inc., Menlo Park, CA.

LEFT ATRIAL APPENDAGE CLOSURE

Intermountain Medical Center was a leading enroller in the PROTECT AF trial of Left Atrial Appendage (LAA) closure as an alternative to warfarin in the setting of atrial fibrillation. The PROTECT AF trial randomized patients to warfarin therapy versus LAA closure via the Watchman® Device (Atritech, Inc., Plymouth, MN). See Figure 5 below. LAA closure met its non-inferiority primary endpoint with a trend towards superiority, suggesting that percutaneous LAA closure was equal in benefit to warfarin therapy (probability of 99%).³

The PROTECT AF trial was reviewed by the FDA's panel of experts in May who voted in favor of approval of the Watchman Device for this indication. Full approval is anticipated in upcoming months.

Our center was selected for ongoing access to this technology in a FDA-supervised registry. Patients with relative bleeding risks, problematic INRs, or lifestyle concerns with warfarin are often selected for LAA closure. However,



Figure 5

The Watchman Device. Image courtesy of Atritech, Inc., Plymouth, MN.

those with absolute warfarin contra-indications cannot be implanted at this time as 6 weeks of warfarin is required following device deployment.

PERIVALVULAR LEAKS

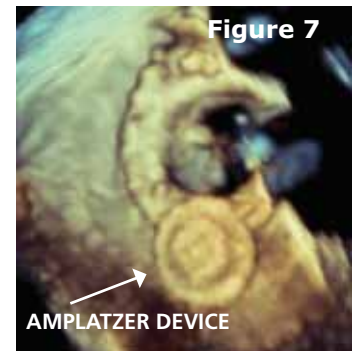
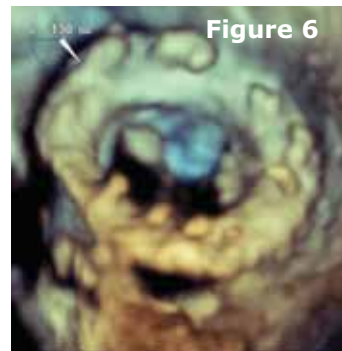
Perivalvular leaks following valve replacement are rare, but present unique challenges to the cardiovascular surgeon. Compromised tissue integrity, which likely led (continued on page 3)

to the initial leak, may predispose patients to poor outcomes with repeat valve replacement. Perivalvular leaks may now be closed percutaneously. The patient in Figures 6 and 7 presented with a history of severe perivalvular mitral regurgitation. This patient received an Amplatzer® ASD (AGA Medical, Plymouth, MN) device delivered to the mitral annulus through the LV apex, which significantly improved the perivalvular regurgitation.

REVIEW

Within a few short years, interventional repair of structural heart defects has boomed and is expanding at an incredible rate. While many of these therapies are in the experimental phase, numerous trials are ongoing and the excitement is palpable. Some of these minimally invasive technologies eventually may become the standard of care, while others will remain an option for high-risk surgical patients.

The Millenium Research Group has predicted that 41% of valve interventions in 2012 will be performed using evolving percutaneous techniques.⁴ An exciting aspect of structural heart



disease care is the demand for a multidisciplinary approach. At Intermountain Medical Center we have seen first-hand the benefits of working together towards the common goal of best patient care.

1. Available at: <http://clinicaltrials.gov/ct2/show/NCT00530894?term=ortic+stenosis&rank=20>.
2. Feldman T, Saibal K, Rinaldi, M, et al. J Am Coll Cardiol. 2009;54:686-694.
3. Holmes DR, Reddy VY, Turi ZG, et al. The Lancet. 374(9689):534-542.
4. Available at: <http://www.mrg.net/>.

HEARTWARE® VENTRICULAR ASSIST SYSTEM – THE ADVANCE TRIAL



PRINCIPAL INVESTIGATOR: BRUCE B. REID, MD
UTAH ARTIFICIAL HEART PROGRAM
1-877-784-2226
WWW.UAHP.COM

The Utah Artificial Heart Program at Intermountain Medical Center is pleased to announce our participation in a new study evaluating the effectiveness and safety of the HeartWare HVAD™ Pump - the only full output, centrifugal, intrapericardial VAD in trial in the United States.

- Intrapericardial - no pump pocket, implantation above the diaphragm may lead to shorter surgery and faster recovery
- Up to 10 L/min of flow
- Small, displaced volume of only 50 cc
- 10 mm outflow graft
- Pump impeller with integrated motor magnets and hydrodynamic bearings which create a passive, noncontacting suspension system
- Approved for use in Europe (Jan 2009) following study at 5 centers, which demonstrated:
 - 90% survival at 180 days
 - 84% survival at 18 months
- Bridge to transplant clinical trial in US – 40 sites enrolling 150 patients
- Appropriate patients have advanced heart failure with NYHA class IV symptoms who are eligible for cardiac transplantation (as determined by transplant center)



Images courtesy of HeartWare, Framingham, MA.

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ROLE OF EXERCISE TRAINING FOR PATIENTS LIVING WITH CHRONIC HEART FAILURE

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It is no longer appropriate for patients living with chronic Heart Failure (HF) to remain sedentary. Numerous clinical, physiologic, and psychological benefits of exercise training in stable HF patients have been documented in recent years.¹ What has not been known until now, however, is whether or not exercise training extends life expectancy or reduces costly hospitalizations.

The impact of exercise training in HF patients was evaluated in the HF-ACTION trial, the largest and longest randomized controlled trial of exercise training for patients with heart disease.² Patients with stable New York Heart Association (NYHA) class II to IV HF with ejection fractions $\leq 35\%$ (n=2331) were randomly assigned to either a supervised exercise training program (n=1159) or usual care that included a general recommendation for regular physical activity (n=1152). The primary end-point was all-cause mortality and all-cause hospitalization. The median age was 59 years. 28%

were women and 37% had NYHA class III or IV symptoms. HF etiology was ischemic in 51%, and median left ventricular EF =25%.

The LDS Hospital–University of Utah site was one of 82 centers in the U.S., Canada, and France participating in this study. Supervised exercise training began in a Phase II cardiac rehabilitation facility with 36 sessions (3 days/week, 30 min/session at an intensity of 60 to 70% of heart rate reserve determined by treadmill exercise testing). After 18 sessions patients were asked to exercise an additional 2 days a week at home using a treadmill or stationary bicycle. This was followed by a structured home exercise program (5 days/week, 40 min/day, at 60 to 70% heart rate reserve). Patients were asked to maintain detailed exercise logs and were contacted frequently by research coordinators to assess compliance to the exercise prescription. Patients were followed for up to 3 years.

There were nonsignificant reductions in the exercise training group for mortality and hospitalizations. After adjustment for major prognostic predictors of the primary endpoint, however, there was a modest and significant decrease for the supervised exercise group in (a) all-cause mortality or hospitalization and in (b) cardiovascular mortality or heart failure hospitalizations (Hazard ratio =0.89; 95% CI: 0.81, 0.99; p=0.03). Serious adverse events were similar in both groups. (continued on page 5)



EFFECTS OF EXERCISE TRAINING IN CHRONIC HF¹

EXERCISE CAPACITY:

- \uparrow VO_{2max}
- \uparrow 6-min walk test
- \uparrow Anaerobic threshold
- \uparrow Maximal exercise duration
- \downarrow Lactate at fixed VO_2
- \downarrow VE at fixed VO_2

CLINICAL INDICES:

- \uparrow Quality of life scores
- \downarrow HF symptoms
- Improved NYHA functional class

HEMODYNAMIC PARAMETERS:

- \downarrow Peripheral vascular resistance
- \downarrow Resting heart rate
- \uparrow Maximal heart rate
- \uparrow Peak cardiac output

SKELETAL MUSCLE STRUCTURE/FUNCTION:

- \uparrow Cross sectional area
- \uparrow Fiber size
- \uparrow Type 1 muscle fibers
- \uparrow Mitochondrial number
- \uparrow Muscle dynamic strength
- \uparrow Capillary density
- \uparrow Aerobic enzyme content
- \downarrow Muscle fatigability

PATHOPHYSIOLOGIC PARAMETERS:

- Improved endothelial function
- \uparrow Heart rate variability
- \downarrow Inflammatory cytokines
- \downarrow QT dispersion
- \downarrow Resting norepinephrine level

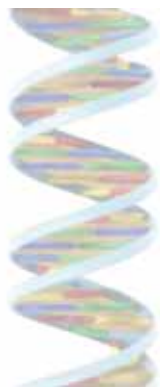
Adherence to the prescribed exercise training regimen during the 36-month trial was a major problem in HF-ACTION. The goal of ≥ 120 min/week was achieved by $< 50\%$ of the study subjects. In a secondary analysis the exercise dose response was studied in the exercise training group.³ When analyzed according to quartiles of exercise duration and intensity, there was a significant improvement in clinical outcomes (mortality and hospitalizations), functional outcomes (VO_{2max} and 6-min walk test), and self-reported health status in subjects achieving the greater volumes of exercise (MET-hour/week).

These findings have important implications for the growing populations of patients living with chronic HF. Thirty minutes of moderate-intensity physical activity most days of the week should be encouraged. The benefits in clinical, functional, and quality-of-life indices will be proportional to the degree of adherence to this recommendation.

1. Witham MD, Struthers AD, McMurdo ME. J Amer Geriatr Soc. 2003;51:699-709.
2. O'Connor CM, Whellan DJ, Lee KL, et al. JAMA. 2009;301:1439-1450.
3. Keteyian SJ, et al. Presented at annual meeting of the American College of Cardiology, 2009.

Upcoming Conference

PERSONALIZED MEDICINE: ARE WE THERE YET?



SATURDAY, NOVEMBER 7, 2009
7:30 AM TO 1:00 PM
AT LDS HOSPITAL

COURSE DIRECTOR:
MARC S. WILLIAMS, MD, FAAP, FACMG
DIRECTOR,
CLINICAL GENETICS INSTITUTE
INTERMOUNTAIN HEALTHCARE

By attending this event, participants will be able to: Define personalized medicine, locate and evaluate information about personalized medicine interventions, describe the impact of pharmacogenomic testing in medication prescribing to improve efficacy and avoid adverse drug reactions, evaluate the current evidence to decide which tests are currently ready for clinical use and which require additional study based on the current evidence, and identify state and national personalized medicine initiatives and the potential impact of comparative effectiveness research.

Welcome New Physicians!

HEART FAILURE AND TRANSPLANT CARDIOLOGY

Rami Alharethi, MD

Heart Failure Prevention & Treatment Program, 801-507-4000



Dr. Alharethi recently joined the staff at the Heart Institute after serving as the medical director of the heart failure and cardiac transplant program at the Oregon Health and Science University. His research interests include advanced treatment of heart failure, cardiac allograft vasculopathy, and mechanical circulatory support. He enjoys hiking, skiing, playing soccer, basketball and tennis. He was just married in September!

Deborah Budge, MD

Heart Failure Prevention & Treatment Program, 801-507-4000

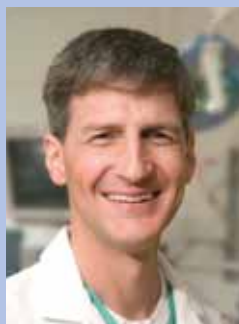


Dr. Budge recently joined the Heart Institute in July after completing her cardiovascular fellowship at University of California Los Angeles. Her clinical and research interests include advanced heart failure, cardiac transplantation, and mechanical circulatory support. She enjoys tennis, hiking, and gardening and just recently bought a home in the Foothill/University area.

CARDIOTHORACIC SURGERY

William T. Caine, MD

Heart & Lung Surgical Associates, 801-507-3600



Dr. Caine joins us from the University of Washington School of Medicine in Seattle where he served as a professor and attending surgeon. His specialties and interests include adult cardiac and thoracic surgery, coronary artery bypass surgery, valve repair and replacement, arrhythmia surgery and neurologic outcomes after cardiac surgery. He is excited to be returning to Intermountain and to friends and family in the Salt Lake area.

INTERVENTIONAL CARDIOLOGY

Edward C. Miner, MD

Intermountain Utah Heart Clinic, 801-507-3500



Dr. Miner joins us after completing his fellowship in Interventional Cardiology at the Texas Heart Institute in Houston. His clinical interests include percutaneous therapy for peripheral vascular disease, interventional cardiology, echocardiography, and nuclear cardiology. He enjoys spending time with his family and playing and watching a wide variety of sports.

CV RESEARCH UPDATE

The CV Research Department at Intermountain Medical Center is currently participating in over 50 clinical trials related to prevention of cardiac disease, coronary artery disease, arrhythmia, and advanced heart failure. We have featured several trials below.

For patients:	Title & description:	Coordinator:
with Acute Coronary Syndrome (ACS) who require coronary angiography with possible intervention	TRACER – A randomized, double blind, placebo-controlled study investigating a direct thrombin inhibitor in patients requiring coronary angiography to treat ACS. The study will evaluate if the patient suffers repeat episodes of ACS. <i>Principal Investigator: Dr. Brent Muhlestein</i>	Eric Johnson <i>Phone: 801-507-4771</i> <i>Pager: 801-242-0221</i>
with Atrial Fibrillation	CABANA – A prospective, randomized, open label clinical trial to compare the difference between catheter ablation versus antiarrhythmic drug therapy for atrial fibrillation. <i>Principal Investigator: Dr. T. Jared Bunch</i>	Michelle Jennings <i>Phone: 801-507-4722</i> <i>Pager: 801-202-1399</i>
newly diagnosed with thrombus	COAG – An NIH, double-blind, randomized study using pharmacogenetic-guided dosing of warfarin, to evaluate the effectiveness of individualized dosing for individuals newly diagnosed with thrombus. <i>Principal Investigator: Scott Stevens, MD</i>	Michelle Robinson <i>Phone: 801-507-4775</i> <i>Pager: 801-241-6271</i>
with heart failure and normal LVEF	RELAX – A double-blind, placebo-controlled trial testing the hypothesis that chronic PDE-5 inhibition improves exercise capacity and clinical status in patients with heart failure. <i>Principal Investigator: A.G. Kfoury, MD</i>	Michelle Endo <i>Phone: 801-507-4762</i> <i>Pager: 801-242-8307</i>

The table above does not provide complete information for each clinical trial. Additional inclusion and exclusion criteria and/or other study requirements apply.

November 2009

FROM THE HEART INSTITUTE AT INTERMOUNTAIN MEDICAL CENTER

THE CLINICAL STATE OF THE HEART

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