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Cardiac Structure and Function

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In the cardiac function and heart failure category, 1,143 abstracts were submitted and 377 accepted for presentation. For clarity, this manuscript will be divided into a number of different highlight subcategories.

Mechanical circulatory assist. Circulatory assist devices have an established role as destination therapy and a bridge to transplantation. Mussivand (1) presented trends in support duration over 10 years in 1,235 patients. The support duration increased from 32 days in 1991 to 196 days in 2002 and was greater in survivors (40 to 284 days) compared with nonsurvivors (26 to 104 days). This suggests there may be a greater emphasis on totally implantable devices in the future, permitting patient discharge.

Maybaum et al. (2) examined cardiac recovery during left ventricular assist device (LVAD) support in a multicenter, prospective study of 64 patients supported for a mean of 166 days. After 30 days, there was significant improvement in the left ventricular ejection fraction (LVEF) (16.6% to 35.4%), left ventricular end-diastolic diameter (LVEDD) (7.2 to 4.8 cm), and left ventricular (LV) mass (321 to 198 g). Three patients with acute heart failure underwent explantation, but no patients with chronic heart failure underwent explantation. The degree of recovery is probably insufficient for device explantation, except in patients with acute heart failure.

Mechanical support in nontransplant candidates was examined in a retrospective review of 225 patients (3). A low-risk category (n =146) was defined by age <65 years, blood urea nitrogen (BUN) <100 mg/dl, creatinine <2.5 mg/dl, bilirubin <5 mg/dl, negative blood cultures, and pulmonary vascular resistance (PVR) <480 dynes · s/cm^5. A high-risk category (n = 44) was defined by one or more discordant values from the low-risk group. The control group (n = 35) met LVAD criteria, but no device was implanted. There was a median survival of 11 days in controls: 197 in the high-risk subjects and 467 days in the low-risk subjects. Twenty-five percent of high-risk patients were bridged to transplant; they had a higher post-implant mortality.

The Tandem Heart (Cardiac Assist Inc., Pittsburgh, Pennsylvania) is a newly developed percutaneous LVAD (4). Twenty patients with acute myocardial infarction (MI) treated with an intra-aortic balloon pump (IABP) were compared with 19 patients treated with the Tandem Heart. Overall, there was a greater improvement in hemodynamic parameters in the LVAD group compared with IABP, but no difference in 30-day mortality (45% for IABP, 39% for LVAD), largely due to LVAD complications. These newer percutaneous devices show promise, but further studies are necessary.

Cardiac allograft vasculopathy. Cytomegalovirus (CMV) infection plays a role in the development of allograft vasculopathy. However, the relationship between the degree of CMV infectious burden and allograft vasculopathy has not previously been examined. Potena et al. (5) presented data on 46 patients, suggesting that the degree of CMV infection is an independent predictor of intimal area increase and progressive allograft vasculopathy.

Statin therapy is not yet routine in the pediatric heart transplant population. Mahle et al. (6) reviewed a total of 129 infants and children who had undergone 142 heart transplants at a median age of 7.3 years. In a multivariate analysis, the use of pravastatin was associated with a significant reduction in the development of allograft vasculopathy (p = 0.03). The authors concluded that statin therapy should now be considered routine maintenance in pediatric cardiac transplant patients.

Data from clinical trials. From the Candesartan in Heart Failure (CHARM) study, the angiotensin receptor blocker (ARB) candesartan was examined for the prevention of type II diabetes mellitus in patients with heart failure (7). A total of 7,601 patients were randomized to 32 mg candesartan or placebo. Of this group, 5,436 had no diabetes mellitus at study entry. There was a significant reduction in the development of new diabetes mellitus with patients receiving candesartan (163 [6%] of 2,715) compared with placebo (202 [7.4%] of 2,721). Candesartan may reduce the risk of developing diabetes mellitus.

The Carvedilol Or Metoprolol European Trial (COMET) compared heart failure outcomes between carvedilol and twice daily metoprolol. Adverse events were less common with carvedilol, including the risk of sudden death, MI, unstable angina, stroke, heart failure, dyspnea, or shortness of breath, as well as the development of diabetes and hypokalemia. However, hypotension, dizziness, and syncope were more common with carvedilol (8). Quality-of-life improvements in the carvedilol group were also noted, as compared with the metoprolol group (9). Patients on higher doses of beta-blockers were found to be younger and have a higher resting blood pressure and heart rate. Administration of a target dose was an independent predictor of lower mortality risk (10).

The Calcium Sensitizer or Inotrope or None in Low Output Heart Failure (CASINO) study examined the novel calcium channel sensitizer called levosimendan for the treatment of low-output heart failure (11). This was a

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multicenter study of 227 patients with an LVEF of <35%, who were assigned to levosimendan (n = 74), dobutamine (n = 76), or placebo (n = 77). The drug was infused for 24 h. The primary end point was a composite of death or re-hospitalization due to heart failure worsening and was reached at six months in 30.6% of the levosimendan group, compared with 52.7% of the dobutamine group and 48.1% of the placebo group.

Heart failure and anemia. Anemia in diastolic heart failure is frequent and associated with a worse outcome, increased brain natriuretic peptide (BNP) levels, and more severe systolic dysfunction. Anker et al. (12), for the Effect of Carvedilol on Survival in Severe Chronic Heart Failure (COPERNICUS) study, reported that anemia was an independent risk factor for adverse outcome in severe heart failure. The mechanism may be due to blunted erythropoietin production, as well as a defective iron supply (13). Altered steroid metabolism with an increased cortisol/dehydroepiandrosterone (DHEA) ratio is a strong predictor of anemia in males with congestive heart failure (CHF) (14). Data from the Study of Anemia in a Heart Failure Population (STAMINA-HFP) registry suggested that anemia is common in CHF seen in specialty and community cardiology clinics (15) and is associated with a reduced quality of life (16).

BNP testing. The BNP testing continues to be of interest for stratification of patients with heart failure. In the Breathing Not Properly multinational study, 227 patients with CHF were followed. There were 51 events, including death and re-admission. Patients with adverse events had higher BNP values at admission and discharge, with fewer adverse events in the patients with a greater degree of BNP decrease (17).

Data on non-terminal (NT) pro-BNP was presented by Mitrovic et al. (18), who studied 523 patients with a mean LVEF of 25% and New York Heart Association (NYHA) functional class II to IV. The NT pro-BNP level was increased as compared with controls and correlated with the BNP level, LVEF, end-diastolic volume, and systolic volume and wall stress, but not with the stroke volume or cardiac output. Nonterminal pro-BNP was also found to be significantly higher in patients who died as compared with those who survived. Also, NT pro-BNP correlates well with BNP and is a predictor of mortality in CHF.

Beta-blockers. Heart failure physicians usually titrate patients up on angiotensin-converting enzyme (ACE) inhibitors before beta-blockade. Krum et al. (19) questioned this strategy in a meta-analysis of available large (n >500), placebo-controlled studies. The results suggested a greater magnitude of prognostic benefit conferred by beta-blockers compared with ACE inhibitors, supporting early introduction.

Massie et al. and the COreg HEart failure REgistry (COHERE) investigators (20) examined the characteristics of heart failure patients by initiating carvedilol and whether they relate to ejection fraction. It was found that age, percentage of women, hypertensive diabetics, and baseline blood pressure all increase with increasing ejection fraction. A lower ejection fraction appears to be associated with a higher NYHA functional class, a greater number of hospitalizations, and greater mortality.

Beta-blockers in the community are used at lower doses than in clinical trials and when prescribed by cardiologists. For the COHERE investigators, Fowler et al. (21) presented data showing that although carvedilol dosing in the community was lower than in trials and was more influenced by NYHA functional class, at all doses, there appears to be a lower incidence of death and heart failure hospitalizations.

Howlett et al. (22) examined whether the mortality benefit of beta-blockers is related to the initial heart rate. A total of 4,888 patients with a discharge diagnosis of heart failure from any Nova Scotia hospital were studied. Beta-blocker prescription at discharge was associated with a 37% lower two-year mortality, regardless of the initial heart rate.

Resynchronization therapy. Resynchronization therapy is established in patients with heart failure and ventricular dyssynchrony. A substudy from MIRACLE, presented by St. John Sutton et al. (23), examined whether reverse remodeling varies with infarct location. Patients in NYHA functional class III and IV heart failure, with an LVEF <35% and with the presence of ventricular dyssynchrony, underwent implantation of the InSync biventricular pacing system. An atrioventricular delay was optimized, and patients were randomized to no pacing or cardiac resynchronization therapy. It was found that there were significant reductions in left ventricular end-diastolic (LVEDV) and left ventricular end-systolic volume (LVESV) in patients who had an inferior MI (n = 28; −43.2 and −43.1 cm^3, respectively). In patients in the anterior MI group (n = 48), changes in LVEDV and LVESV were 1.6 and −5.3 cm^3, respectively. This was despite improvements in LVEF and mitral regurgitation in both groups. The investigators concluded that the infarct location determines the extent of remodeling in heart failure patients treated with cardiac resynchronization therapy.

Use of cell therapy in CHF. This remains an evolving area. Which cell type to use has not yet been established, and the studies presented have reinforced this controversy. Perin et al. (24) examined transendocardial injection of autologous bone marrow mononuclear cells. Fourteen patients with ischemic cardiomyopathy were treated with transendocardial injection of cells into a target area, defined as a reversible defect by single-photon emission computed tomography (SPECT) with viability by electromechanical voltage mapping. A control group of six patients had no intervention. In the injected area, there was no difference in voltage at baseline and four months. However, there were significant differences in voltage in the peri-infarct area. The authors concluded that this increase in voltage may represent expansion in myocardial viability. The same study

group found that within two months of stem-cell injection, there were significant reductions in the total reversibility of the defect (15% to 5%, p = 0.022), as well as an improvement in the ejection fraction (30% to 35%, p = 0.02) and NYHA functional class (2.21 to 1.14) (25).

Dib et al. (26) presented the results of a multicenter study in which autologous skeletal myoblast transplantation was performed at the time of coronary artery bypass grafting (CABG) in patients with a previous MI and LVEF <40%. All patients underwent a 2-g muscle biopsy to expand myoblasts. Subsequently, 3 to 30 injections were performed into the infarct area with 10 to 300 million cells. A total of 22 patients underwent this procedure, combined with CABG. Echocardiography, positron emission tomography, and magnetic resonance imaging studies showed viability in the grafted scar, and there was an increase in LVEF from 24.8% to 33.9% (p = 0.04) in 10 patients. The procedure appears to be feasible and safe, but it is unclear whether the benefit was due to skeletal myoblast transplantation or CABG.

Myocarditis. Myocarditis following smallpox vaccination was presented by Dr. Eckart from the Army Medical Centers (27). Fifty-three military personnel developed probable acute myopericarditis following smallpox vaccination. In these patients, troponin I was elevated on presentation (10.5 ± 23.4 ng/ml) and remained elevated to a similar level for up to 48 h, with a peak troponin I level of 14.8 ± 26.5 ng/ml at a median of 6.7 h. Creatine kinase (CK) and CK-MB were also elevated within 24 to 48 h, with a peak CK-MB level of 438 ± 339 at a median of 5.9 h. Vaccinial myocarditis may therefore present as sustained elevation of cardiac enzymes for up to four days.

Hypertrophic cardiomyopathy. Ommen et al. (28), from the Mayo Clinic, examined the long-term effects of surgical myectomy in 1,337 patients evaluated between 1983 and 2001. This is the largest study examining this subject. Of these patients, 289 underwent isolated surgical myectomy for LV outflow tract obstruction; 228 were managed without surgery; and 820 had nonobstructive hypertrophic cardiomyopathy. Survival rates at 1, 5, and 10 years were 98%, 96%, and 83%, respectively, in the group that had undergone myectomy, which is no different from the control population of patients with nonobstructive hypertrophic cardiomyopathy. Myectomy patients have a better survival than nonoperated, obstructed patients. The authors concluded that myectomy reduces the excess mortality risk associated with outflow tract obstruction.

The mechanism of systolic anterior motion of the mitral valve following septal ablation was examined by Nesta et al. (29) from the Massachusetts General Hospital. The echocardiograms of 30 patients were reviewed before and three months after septal ablation, and it was concluded that persistent systolic anterior motion was largely due to anterior malposition of the mitral valve.

Van Driest et al. from the Mayo Clinic (30) examined sarcomeric mutations in hypertrophic cardiomyopathy. The frequency spectrum and phenotype in patients with complex genetic status (more than one sarcomeric mutation) was examined. Of 389 patients, 151 (38.8%) had at least one putative pathogenic mutation. Eleven patients (2.8%) had two putative mutations, and these patients were younger at diagnosis, with a greater degree of hypertrophy, and more frequently had an implantable cardioverter-defibrillator (ICD). Multiple sarcomeric mutations result in a greater degree of hypertrophy and an earlier diagnosis of hypertrophic cardiomyopathy.

Peripartum cardiomyopathy. Tallaj et al. (31), from Birmingham, Alabama, examined outcomes in peripartum cardiomyopathy in the current era, with a retrospective chart review from 1990 to 2000. Of 37 patients with peripartum cardiomyopathy, 81% were in NYHA functional class III/IV, with an LVEF of 23 ± 11%. Thirty-two patients were treated with ACE inhibitors, nine with angiotensin receptor blockers, 17 with beta-blockers, as well as digoxin (76%), diuretics (89%), spironolactone (33%), nitrate (6%), and warfarin (41%). Four patients underwent heart transplantation; one patient died; and one was lost to follow-up. Ninety percent (25 of 31) were in NYHA functional class I/II, with an LVEF of 40 ± 16% (42% of patients had normalized their ejection fraction). Although, historically, peripartum cardiomyopathy does not have a good outcome, the prognosis appears to be significantly better than that previously reported.

Late-breaking clinical trials. The WATCH study sought to clarify the role of anticoagulation in CHF patients in normal sinus rhythm. The study was a three-arm, randomized trial of open-label warfarin (with an international normalized ratio maintained at 2.5 to 3.5) or double-blinded antiplatelet therapy with 162 mg aspirin or 75 mg clopidogrel. All patients had an LVEF <35% with symptomatic CHF and ongoing treatment with ACE inhibitors and diuretics. A total of 1,587 patients were enrolled. There was no significant difference in the primary end point of all-cause mortality and nonfatal MI or stroke. However, there were a higher number of hospitalizations and exacerbations due to heart failure in the aspirin group and fewer heart failure hospitalizations in the clopidogrel group. The study reinforced the concept that the use of aspirin in patients with heart failure treated with ACE inhibitors may be deleterious.

The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) study examined amiodarone or ICD therapy compared with placebo in NYHA functional class II and III CHF. A total of 2,521 patients were enrolled from September 1997 to July 2001, and followed until the end of October 2003. The primary specific aim was all-cause mortality. The three arms were: 1) conventional CHF therapy and placebo; 2) conventional CHF therapy and amiodarone; and 3) conventional therapy and single-lead ICD. The five-year survival rates were 28.9% for the ICD group, 34.1% for the

amiodarone group, and 35.8% for the placebo group. For patients with NYHA functional class II or III CHF with an LVEF <35% on good background therapy, mortality for the placebo-controlled patients was 7.2% per year over a five-year period, and a simple shock-only ICD decreased mortality by 23%. Amiodarone, when used as a primary preventative agent, does not improve survival.

The Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) study examined prophylactic ICD therapy early after acute MI (4 to 40 days) with an LVEF <35% and evidence of impaired cardiac autonomic modulation. A total of 674 patients were randomized, 332 of whom received an ICD; 65% of the patients were reperfused and 90% were treated with optimal medical therapy. The primary aim was all-cause mortality, with a mean follow-up of 30 months. There was no difference in the primary end point for optimal medical therapy (6.9%) or for medical therapy and ICD (7.5%). However, there was a decreased incidence of arrhythmic death in the ICD group (1.5% vs. 3.5% annual mortality). In addition, there was an increased incidence of nonarrhythmic death in the ICD group.

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