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Summary of 2019 Brano Heart Failure Forum Presentations

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Abstract

The Branislav “Brano” Radovancevic Heart Failure Forum (BHFF) was established in 2008. Each year, experts in the field of heart failure gather to learn, discuss and debate the recent advances and theories related to diagnostics and therapeutics. The 12th Annual BHFF was held September 18-21, 2019, in Belgrade, Serbia, and was attended by over 350 participants from 15 countries. Over four days, seventeen separate sessions focused on challenges and solutions related to mechanical circulatory support and heart transplantation. For the first time, a summary of selected presentations was organized and presented herein.

Mechanical Circulatory Support and Heart Transplantation

Over the past sixty years, there has been considerable progress in developing durable mechanical circulatory support (MCS) systems. Multiple international MCS registries report data from patients receiving durable MCS devices in all participating countries and hospitals.[1, 2] INTERMACS and PediMACS (US), EUROMACS (Europe), J-MACS (Japan), and UK MCS Registry (United Kingdom) have combined data input into the ISHLT (IMACS) Worldwide Registry. Data from almost 20,000 patients have been entered into this registry. Trends in survival rates continue to rise, with 1-year survival at 90% and 4-year survival at 54%. The improving survival is attributed to a decline in adverse event rates. Novel energy transfer systems for durable left ventricular assist devices (LVAD) represent the latest advances that will likely continue improving outcomes.

Heart transplantation remains the treatment of choice for end-stage heart failure, but serious challenges remain. Limiting heart transplant factors include donor shortages, allograft vasculopathy, complications from immunosuppression, antibody-mediated rejection, and increasingly complicated recipients. Future alternatives to heart transplantation may involve durable LVADs, xenotransplantation, stem cell therapy, and whole-organ bioengineering. Ex-vivo organ preservation systems can improve donor allocation by allowing up to 12 hours of donor organ preservation.[3] Needed improvements in post-transplant patients include avoidance and treatment of allograft vasculopathy, malignancies, renal dysfunction, and better immunosuppression.

Despite advances in medical therapies to treat heart failure, the hospitalization rate has not changed significantly since 2000. Heart failure continues to be a significant driver of overall health care costs, with the global cost estimated to increase to $170 billion by 2030. Nearly every new payment model requires hospitals and physicians to work collaboratively with mutual accountability for long-term quality and costs. Hospitalization accounts for 50% of this cost, and with all-cause readmission rates of 50% within 6-months, improving out-of-hospital care is crucial.[4-6] Real-world use of the CardioMEMS™ HF System reduces heart failure hospitalizations and comprehensive hospitalization costs. Focusing on the economic processes within a program should lead to cost savings and revenue increases. Understanding how much money each cardiovascular (CV) service contributes per day helps hospital administration know what to resource appropriately.

As the prevalence of heart failure continues to rise worldwide, research and development of novel therapies is a continuing challenge. Researchers need to be aware of the spectrum of funding sources and obtain funds for basic and applied research programs. Phase III trials in the global setting are needed, but there

needs to be a focus on Phase I and Phase II as well. Investment in single-site investigations, which are the foundation for the Phase III trials. Heart failure needs well-designed trials to reduce the failure rate of Phase III studies.

Important Elements of a Successful MCS and Heart Failure Program

The established goals of heart failure management are improving symptoms and quality of life, slowing the progression of CV dysfunction, and reducing mortality. Keys to successful treatment are to employ a multidisciplinary approach, properly select patients for treatments, comprehensive patient management, and provide psychosocial support. Improved outcomes will result from improvements in patient selection, technology, and patient management. LVADs improve survival, health-related quality of life, and functional status but are associated with major adverse events in a substantial percentage of patients. The incidence of adverse events varies between devices and by the indication for LVAD implantation. Reducing device-related complications in the future requires control of risk factors, improved surgical implantation techniques, and advances in LVAD technology.

Gastrointestinal (GI) bleeding is the number one cause of hospital readmission in outpatients with LVAD support.[7] Approximately 20% to 40% of patients supported by a CF LVAD bleed from the GI tract (7.8 events/100 patient-months).[8] All anticoagulants should be discontinued upon admission for GI bleeding and are restarted after complete resolution of bleeding with a targeted INR towards the lower end of the range. Aspirin is usually restarted after the cessation of GI bleeding. Octreotide is capable of stabilizing GI bleeding by causing splanchnic vasoconstriction and improved platelet aggregation.[9, 10]

The development of right ventricular failure (RVF) in LVAD recipients is associated with increased morbidity and mortality. The preoperative state of the right ventricle (RV) is important to establish. RVF exists in approximately 25%-40% of patients with implanted LVADs. The incidence of RVF after LVAD placement is difficult to assess due to the lack of a common definition. Communication among the perioperative team may be beneficial for the early initiation of temporary right-sided MCS to avoid RVF-related complications.

Levosimendan (calcium sensitizer) has a positive inotropic effect by increasing the affinity of myocardial troponin C to calcium and does not occur at the expense of calcium overload or increased myocardial oxygen demand. Vasodilation occurs in both arterial and venous smooth muscle cells, causing reduction in both RV preload and afterload. There is cardioprotection by reducing ischemia-reperfusion

injury, apoptosis, and oxidative stress. Levosimendan has a favorable inotropic and vasodilatative effect on RV function and systemic circulation for several days in LVAD patients.

Patients with congenitally-corrected transposition of great arteries (ccTGA) often present with heart failure in the fourth or fifth decade of life. Implantation of an LVAD in the systemic ventricle has been described in small groups of patients. Accurate imaging (transthoracic echocardiography [TTE] with contrast, transesophageal echocardiography, and cardiac multi-slice computed tomography) is essential in successfully implanting small-sized intrapericardial LVADs in patients with complex anatomies, such as ccTGA and dextrocardia. Implantation is technically challenging but feasible.

Mitral valve (MV) repair along with coronary artery bypass graft (CABG) surgery in patients with severely depressed LV function provides favorable midterm survival results. Frequently, the MV has some degree of papillary muscle dysplasia and leaflet underdevelopment that goes undiagnosed by echocardiography exam or during valve analysis. The incidence of papillary muscle dysplasia and leaflet underdevelopment increases with ischemic heart disease. This is the reason that a reduction annuloplasty in patients with severely depressed LV function has a high mitral regurgitation (MR) recurrence. To choose the appropriate repair technique in patients with severely depressed LV function, the subvalvular apparatus and leaflets should be carefully examined.

Update on Regional End-Stage Heart Failure Program

Brief reports on the status of durable and short-term MCS and heart transplantation were given for centers in Italy, Hungary, Croatia, Macedonia, Slovenia, and Serbia. Generally, the volume of these therapies is increasing at a fast pace with improving outcomes.

Heart Failure Management

There are many unmet needs in the management of acute and chronic heart failure. The prevalence of advanced heart failure in the United States is now estimated at 5.7 million people and is expected to increase by 46% in the next ten years.[11] Opportunities for improvements in therapy for advanced heart failure include innovative new drugs, increasing the donor heart pool, and expanding the application of MCS. Opportunities for improving the care of cardiogenic shock involve earlier use of MCS, safer technology, and more durability.

Current heart failure management involves attention to MV function. Approximately 20% of patients admitted with advanced heart failure have moderate to severe MR. First-line therapy is optimal medical management; for persistent degenerative MR, surgery is necessary. Patients with 3+ MR despite medical therapy should be assessed for percutaneous therapies. There are numerous evolving treatment options for functional MR.[12]

No two advanced heart failure patients are the same, which requires diverse, individualized therapy regimens that consider underlying etiology, patient preferences, genotypes, and financial realities. Medical therapies needs include a safe oral inotrope, a simpler oral vasodilator, better antiarrhythmics, and drugs that decrease the heart rate. Cardiac resynchronization therapy (CRT) needs to be refined by determining which patients will benefit from the therapy, optimal lead placement, and optimal device settings. MCS continues to evolve to improve the quality of life. Regenerative and replacement therapies continue to improve and play an expanding role in the treatment regimens. For 2019, biologic replacement of the heart remains the best option.

EUROMACS is a large international registry of data from patients supported by durable MCS that enables clinical research.[13] Regular reports enable comparisons among participating centers and other registries. There are 71 participating centers in 21 countries with over 5000 patient entries. Pediatric patients comprise 6.5% of all patients, and 81% are males. Indications for LVAD implantation include bridge to transplant (36%) or to candidacy (33%), destination therapy (15%), rescue (7%), recovery (4%) and other (5%). Major infection (48%) and bleeding (20%) are the most frequent adverse events reported. Ten publications report the details from this registry.

Hot Topics in Heart Failure

There are a number of challenges related to recovery after temporary MCS. Currently, there is no clear definition of myocardial recovery. Objective measures for clinically meaningful ventricular unloading that will optimize recovery are needed. There is a need for novel MCS device designs and control strategies that could enhance myocardial recovery. Objective measures of unloading and reloading of myocardium using advanced imaging modalities and sensors, metabolic techniques, and physiological data need to be defined. Recovery rates with LVADs are highly variable, and post-explant outcomes appear heterogeneous. Comparisons of studies are difficult because of differing heart failure etiologies, durations of failure, follow-up periods, patient selection, weaning strategies, and definitions of recovery.

Recovery of myocardial function during LVAD support provides insight into the inflammatory triggers in heart failure. Multiple inflammatory pathways are active during the injury phase and during repair. During LVAD support, decreasing inflammation is a very strong signal of the repair process. Inflammatory responses activate epithelial mesenchymal transition hat contributes to fibrosis during heart failure. Inflammation is a dynamic process in the progression of heart failure. Myocardial samples taken before and after LVAD procedures are of great value to study the biology of human heart failure.

The REVIVE-IT clinical trial was designed because an unmet clinical need exists for heart failure patients who remain symptomatic with a depressed ejection fraction despite conventional medical therapy.[14] Equipoise exists for designing a clinical trial with circulatory assist devices in less-ill patients with the current generation of LVADs. However, equipoise was disrupted by concerns over adverse events. In the current state of MCS technology, with the exception of right heart failure, better “risk” status at implant provides limited or no “protection” against serious adverse events. The major advantage of an LVAD over medical therapy is in the quality of life; however, ischemic stroke is six times more common and hemorrhagic stroke is three times more common in LVAD vs medical therapy. Equipoise for another clinical trial requires continued improvement in stroke reduction with a stroke rate close to 5%.

Acute MCS

Extracorporeal membrane oxygenation (ECMO) is the best option in acute cardiopulmonary failure because it can be:

- applied for cardiac and pulmonary failure
- converted to cardiopulmonary bypass for subsequent surgery
- converted to temporary LVAD or RVAD
- converted to RVAD after permanent LVAD implantation
- used for varying durations
- less expensive than other therapies
- used for bridge to decision, bridge to recovery, bridge to transplant, or bridge to durable LVAD [15]

Based on experience in Croatia, ECMO should be a nationwide primary resuscitation tool as it is lifesaving with a very favorable success rate. Because timing of implantation is critical, this lifesaving opportunity should be funded by the national healthcare system, and intensive and aggressive education should be organized nationwide to utilize all of the potential of the technology.

Anticoagulation during ECMO support normally includes an initial bolus of 5,000 to 10,000 units of heparin and maintenance infusions to maintain the activated clotting time (ACT) at 180 to 200 seconds and the partial thromboplastin time (PTT) at 60 to 80 seconds. The negative effects of heparin include excessive bleeding when the PTT is greater than 90 seconds, heparin-induced thrombocytopenia in 5% of patients and a reduction in antithrombin levels. Platelet activation occurs due to high shear stress, mostly at tubing connecter sites. Studies indicate that low does or discontinuation of heparin during ECMO is feasible in some patients, but this requires more research.

LV distension due to increased afterload during VA-ECMO can result in pulmonary edema and poor myocardial recovery. Venting of the LV with an Impella device (Abiomed) during veno-arterial (VA) ECMO support may alleviate LV distension; however, the benefits of this approach are unknown. Patients receiving an Impella device that are later escalated to VA ECMO support demonstrated significantly lower mortality than patients who received VA ECMO support first. Patients who require cardiopulmonary resuscitation before Impella or VA ECMO have the worst survival. The beneficial effects of a primary versus secondary LV unloading strategy with the Impella device has to be evaluated in prospective, randomized trials.

The use of an Impella 5.0 device as a bridge-to-bridge in patients classified as INTERMACS profile 1 may offer a survival benefit. At Memorial Hermann Hospital, the percentage of patients in INTERMACS profile 1 before LVAD implantation is considerably higher than reported in the INTERMACS Registry (42% vs. 18%);[15] however, the short- and long-term survival rates are equivalent. Despite inotropic support, many patients cannot be hemodynamically stabilized and have refractory low-cardiac output. Long-term assist devices are an expensive option, and their implantation is complicated by a high rate of right heart failure and mortality. Bridging patients with a short-term MCS is intended to stabilize hemodynamics and improve end-organ function. This tactic may improve survival and reduce surgical risk as more time is allowed for a thorough evaluation of options and prognosis.

For patients who are stable on acute MCS but require continuous support, there are a variety of options with different expected outcomes. A durable LVAD or heart transplant may be suitable for select patients, but major surgical risk, organ availability, and known complications may limit those options option. Ambulatory support with the Intravascular Ventricular Assist System (iVAS) uses a minimally invasive technique and has a short recovery time. The iVAS can be stopped temporarily, maintenance and troubleshooting are non-emergent, and there is no need for a continuous caregiver. During support, the iVAS increases coronary blood flow, decreases left ventricular afterload, and promotes myocardial recovery.

A select group of patients with myocardial reserve can be supported for long durations, rehabilitated, and discharged from the hospital.

Frailty is the state of increased vulnerability to physiologic distress and is distinct from aging, comorbidity and disability. A specific frailty measure needs to be developed and validated for the advanced heart failure population. The tool should measure typical features of frailty and assist in distinguishing heart failure-related debility versus frailty-related debility. Ideally, the measure of frailty would predict clinical outcomes after LVAD and the rehabilitation potential of patients. There is a growing population of older adults being considered for transplant or LVAD candidacy. While multiple frailty scores exist, there is not a broad consensus on how and when to use them. Further, many are burdensome – either in manpower, time or tools. Presently, there is a lack of evidence for frailty measures efficacy in the advanced heart failure population.

LVAD Complications

von Willebrand Factor (vWF) is a multimeric protein that binds collagen on vascular sub-endothelium and platelets. High molecular weight multimers (HMWM) of vWF are more active in mediating platelet adhesion and aggregation. Acquired von Willebrand Syndrome (AvWS) is a disorder characterized by decreased HMWM. Loss of vWF HMWM is attributed to shear damage in LVADs and is associated with GI bleeding during support with axial and centrifugal flow LVADs. Degradation of vWF HMWM was seen in both types of pump with significantly greater preservation of vWF HMWM seen with HeartMate 3 (Abbott) compared to HeartMate II (Abbott). Functional attributes of vWF (antigen and activity) are within normal range post-LVAD, although “normal” values post-LVAD may need to be defined. vWF HMWM alterations, but not functional changes, are closely correlated with episodes of bleeding and non-surgical bleeding in HeartMate 3. There is emerging evidence of angiotensin inhibition and incidence of GI bleeding during LVAD support. GI bleeding is common during LVAD support and is observed in 25% - 40% of patients. The significant morbidity from GI bleeding includes blood transfusion with allosensitization and the potential increase in thromboembolic events. GI bleeding is associated with hospitalization, reduced anticoagulation intensity, and the need for blood product transfusion. Angiotensin II antagonism is associated with a reduced risk of GI bleeding caused by arteriovenous malformations in patients supported by an LVAD.[16] Studies indicate that angiotensin II receptor blockers or angiotensin converting enzyme inhibitors should be prescribed to patients with the continuous flow (CF) LVADs to reduce afterload and potentially reduce GI bleeding.[17] Further study should be randomized and focus on comparative efficacy between therapeutic classes of medications.

GI bleeding is the most common cause of morbidity and rehospitalization in patients supported by a CF-LVAD. GI bleeding decreases the quality of life and increases the risk of thromboembolism. Gastrointestinal angiodysplasia (GIAD) are leaky, proliferative, thin-walled vascular channels without adequate pericyte support and account for 5% of the GI tract's bleeding lesions in the general population. GIADs are responsible for 60% of confirmed GI bleeding in patients with CF-LVADs. Inhibition of the HIF1a pathway with digoxin restores the balance of angiogenic factors with a decrease in Ang-2 and VEGF and an increase in Ang-1. Digoxin may prevent GIAD-related bleeding in CF-LVAD patients by preventing pathological angiogenesis in intestinal mucosa and stabilization of preexisting lesions.

Based on the German Heart Center Berlin experience, a comparison of adverse events and outcomes between the HeartWare ventricular assist device (HVAD, Medtronic) and HeartMate 3 was reported. The HVAD supported over 900 patients, and more than 160 patients received the HeartMate 3. The rates for pump thrombosis, cerebral bleeding, and total stroke were significantly better for the HeartMate 3, whereas the driveline infection rate was lower for the HVAD supported patients. The rate of GI bleeding was not different between the two devices. The HVAD was associated with more cerebral bleeding and pump thrombosis than the HeartMate 3, resulting in a higher hemocompatibility-related adverse event score, especially after one year of support. The HeartMate 3 had a higher rate of outflow graft twist. The overall survival rate was similar between the two devices.

Challenges in Mechanical Circulatory Support

One cause of driveline failure in the HeartMate II is damage to the percutaneous lead's wiring insulation resulting in an electrical short to ground, referred to as a short-to-shield (STS). When there is a break in the outer insulation of one of the conductors, there is the potential for unintended electrical contact between the wire strands and the metal-braided shield, resulting in an STS. This condition can result in speed reduction and pump stoppage when the pocket controller is connected to an alternating current or a grounded power source such as the mobile power unit and power module. Nearly 15% of patients implanted with the HeartMate II have experience percutaneous lead damage.[18] Since pump replacement is usually not associated with high mortality, it should be considered, especially in destination therapy patients. Patients and their families need to be well informed regarding the benefits and risk of LVAD replacement versus staying with an ungrounded cable.

Complex infections during support with an LVAD are difficult to manage and add to the cost of care. For severe device infections, the first priority is drainage and debridement of the infected site. The second priority is microbial suppression and sterilization with supplemental topical means, including irrigation and lavage systems. Antibiotic beads may be effective in treating severe LVAD site infections. Omental flaps to vascularize the infection site have also been shown to be effective in some patients.

During LVAD support, pumping integrity depends on competent native heart valves. The International Soceity of Heart and Lung Transplantation Guidelines recommends that patients with more than mild aortic insufficiency should promptly be considered for surgical intervention during device implantation. The incidence of aortic insufficiency is high in LVAD-supported patients (37%).[19] For severe aortic regurgitation, the aortic valve may be closed at implantation.[20] Tricuspid valve regurgitation should be corrected, especially if atrial fibrillation, a dilated annulus greater than 42 mm, and a small left ventricle are present. Some patients will continue to have or develop MR after LVAD implantation, which negatively affects RV function, LVAD filling, and possibly survival. Acquired aortic insufficiency is better tolerated with a competent MV. Mitral repair associated with LVAD support does not increase operative mortality, reduces long-term MR, and can decrease RV failure rates.

Appropriate treatment of biventricular failure requires specific considerations during the assessment phase. Biventricular failure is common in many patients that present with advanced stage heart failure. The diagnosis of biventricular failure involves elevated right atrial pressure, peripheral edema, renal dysfunction, and hepatic dysfunction. Patients with biventricular failure are in INTERMACS profile 1 or 2 with treatment consisting of ECMO, intra-aorta balloon pump, and multiple inotropes. In determining the appropriate treatment approach, candidacy for transplant or destination therapy should be considered. The etiology and reversibility of failure should be determined, and the most appropriate MCS device for meeting the ultimate goal must be carefully chosen.

Challenges in Heart Failure Interventions

Implantable cardioverter defibrillators (ICD) are recommended to reduce the risk of sudden death in select patients with heart disease. The risk of sudden death has been reduced by 44% since the introduction of ICD therapy and the implementation of new heart failure medications. Prophylactic ICDs in patients with symptomatic, non-ischemic heart failure is not associated with a significantly lower long-term rate of all-cause death. The association between ICD use and survival

decreased linearly with increasing age. ICD for primary prevention is underused, although it is associated with reduced short- and long-term all-cause mortality. In the STICH trial, patients with an ejection fraction <35% and coronary artery disease amenable to CABG were randomly assigned to medical therapy alone (602 patients) or medical therapy plus CABG (610 patients). The primary outcome was the rate of death from any cause. Secondary outcomes included death from CV causes, death from any cause, and hospitalization for CV causes. There was no significant difference between medical therapy alone and medical therapy plus CABG with respect to the primary endpoint. Patients assigned to CABG had lower rates of death and hospitalization. In patients with ischemic cardiomyopathy, the primary and secondary outcomes were significantly lower over ten years among patients who underwent CABG in addition to receiving medical therapy than those who received medical therapy alone.

Clinical trials studying transcatheter aortic valve implantation (TAVI) have mostly involved older patients; however, this treatment may be suitable for younger patients. Guidelines include comprehensive diagnostic and treatment options, multidisciplinary teams, networking among hospitals, strong communication structure, and regular assessment of various interventions. Ongoing investigations are destined to expand indications for TAVI towards lower-risk, younger, and asymptomatic populations. Before TAVI can be widely used in younger patients, it must demonstrate long-term durability equivalent to surgical bioprostheses. Strategies are needed for managing structural valve deterioration, reducing the requirement for permanent pacemaker implantation, and ensuring minimal incidence of paravalvular leak. Overall, TAVI appears poised to be the preferred strategy for aortic valve replacement in most patients.[21]

Percutaneous mitral interventions are variable in outcomes as there are numerous mitral devices and ongoing clinical trials. In the MITRA-FR clinical trial, patients with severe MR and ineligible for mitral surgery were randomized between MitraClip (Abbott, Chicago, IL) plus medical therapy or medical therapy alone.[22] No difference was observed in the composite endpoint of all-cause death and rehospitalization for heart failure. The COAPT trial, a multicenter trial in patients with heart failure and moderate-to-severe (3+) or severe (4+) secondary MR who remained symptomatic despite maximally-tolerated guideline-directed medical therapy (GDMT) were also randomized between MitraClip plus GDMT or GDMT alone.[23] In this study, there was a significant difference in all-cause mortality and hospitalization favoring the MitraClip plus GDMT. Continuing studies evaluating various devices and techniques are necessary to define the utility of percutaneous mitral interventions better.

The best surgical treatment for secondary MR remains controversial. Mitral repair performed with an undersized rigid complete ring to restore leaflet coaptation and

valve competence has been considered the standard treatment. This procedure can be performed with acceptable perioperative risk in carefully selected patients with secondary MR and poor LV function. Several predictors of failure after repair have been recognized in the last decade, and it is well known that more advanced leaflet tethering predicts significant recurrence. To improve MV repair durability, concomitant techniques on the subvalvular apparatus have been described. Small, non-randomized, and observational studies have assessed secondary chordal resection suturing of the posteromedial papillary muscle to the aorto-mitral continuity, infarct plication, papillary muscle imbrication, and posteriori LV restoration. No study has convincingly demonstrated a survival benefit compared with medical therapy in patients with MR and LV systolic dysfunction; this argues against surgical intervention in asymptomatic patients and poses a complex surgical decision in high-risk cases.

MCS Management

Multimodality imaging is necessary to guide LVAD patient management. Computed tomography (CT) is useful to detect thromboembolism, aortic root thrombus, outflow graft twist or link, in flow cannula malposition, or pump thrombosis. TTE helps to assess RV failure, cardiac tamponade and inflow cannula malposition. Positron emission tomography/computed tomography (PET/CT) can identify infections of the driveline, pump pocket, and LVAD components. Outcomes of LVAD supported patient may be enhanced with defined image acquisition protocols and surveillance, interpretation protocols aligned with current standards and prospective multicenter studies to better understand the impact on outcomes. Echocardiography remains plays a critical role to determine ventricular size/function, valvular function and resting intra-cardiac hemodynamics. Preliminary observational data suggest strategies aimed at optimizing hemodynamics while on LVAD support meaningfully impacts quality of life and clinical outcomes. Cardiac CT permits visualization of the inflow and outflow cannula, aortic root and intra-cardiac structures. PET/CT imaging provides accurate information on the location and extent for LVAD specific or related infection and has clinical management and outcome implications.

Left ventricular flow dynamics, unloading, and risk of thrombosis are influenced by LVAD inflow cannula placement.[24, 25] Techniques for 3D printed exoskeleton of the LVAD inflow cannula can guide proper positioning of the cannula. Personalized, reproducible and standardized method for optimal inflow cannula position has been evaluated clinically with positive results. Computer-aided individual patient specific 3D reconstruction of the complete left ventricle and Computational Fluid Dynamic (CFD) and 3D printing was used. The method can be used with every

surgical technique and all types of LVADs. This method should allow for increased patient safety and widen LVAD indications to lower risk patients.

The theoretical benefits of avoiding cardiopulmonary bypass during LVAD implantation are a reduction in inflammatory activation, consumption of coagulation factors, and less bleeding that minimizes blood transfusion, pulmonary vascular resistance and right heart failure. Also, shorter operative and hospitalization time may lead to better survival. Off-pump LVAD implantation has a number of limitations that limit ability to address anatomic and surgical issues. Clinical studies indicate that off-pump LVAD implantation is feasible and technically not too challenging. There is less postoperative bleeding which may lead to less right heart dysfunction, improved outcomes and shorter length of hospital stay. New surgical tools may improve the technique of off-pump implantation.

In a randomized clinical trial, heart failure hospitalizations were less in patients managed with guidance from an implantable pulmonary artery pressure sensor (CardioMEMS) compared with usual care.[26] The 12-month survival rate is significantly better for patients monitored by the CardioMEMS device. Trends in pulmonary artery pressure allow for careful management of heart failure therapy that avoids decompensation and hospitalization. Future application of the CardioMEMS technology with continuous pulmonary artery pressure monitoring incorporated with LVAD support may offer the ability to support patients with a “smart pump”.

Total implantation of durable MCS systems with coplanar energy transfer (CET) have the potential to improve outcomes of LVAD supported patients by elimination of the percutaneous driveline.[27] Energy to power LVAD pumps is transferred across the skin to an internal coil ring and to a battery. Two initial implants have been performed as a bridge to transplant with the Jarvik 2000 LVAD. One patient was discharge from the hospital and eventually underwent successful heart transplant. The second patient suffered a stroke and had the LVAD decommissioned. The CET system functioned without significant problems in both patients.

Novel Technologies

The development objectives for MCS at Abbott is to reduce adverse events, improve patient’s quality of life, decrease surgical complexity and improve patient’s medical management. The basis for improved hemocompatibility is with full MagLev technology in the CentriMag and HeartMate 3 devices. The HeartMate Touch™ Communication System is designed to be simple, robust and intelligent

using wireless Bluetooth technology. Communication through the Merlin.net Patient Care Network will allow for remote patient monitoring of patients with MCS. Incorporation of continuous pulmonary artery pressure monitoring with the HeartMate 3 and enhanced communication leads to “smart pump” applications in the future.

The focus of MCS research and development at Medtronic is to improve patient experience and management, reduce adverse events, and improve patient’s quality of life. The philosophy behind the new peripherals is to improve the patient experience and safety. The controller and battery are integrated into one unit which improves patient usability and significantly reduces weight. Patient experience is enhanced with actionable warnings and ease of use. The new peripherals will be Carelink connected for remote patient monitoring. Carelink enables remote access to waveforms, logfile data and device operating parameters. A fully implantable LVAD system is being developed and incorporates multiple components including implantable rechargeable battery, telemetry, and microelectronics.

The Syncardia Total Artificial Heart (TAH) is now available in 50cc and 70cc sizes and there are three models of system drivers. The 50cc model is most suiotable for small adults and pediatrics. One of the major limiting factors in TAH adoption is the perceived debilitating quality of life caused by the current Freedom driver system. The new generation Freedom XQs offers a vast upgrade to its predecessor, eliminating the value proposition of a better quality of life that VADs offer and consequently, should dramatically improve TAH usage.

The Realheart TAH is based on the action of the natural atrio-ventricular valve plane motion for efficient cardiac function. Bench, laboratory testing and animal studies over the past 20 years have produce a well-functioning TAH system. There is low shear stress, low areas of blood flow stagnation, and there is good hemocompatibility. Twenty-six large animal studies have been completed showing adequate hemodynamic support and this is a silent pulsatile pump, cardiac output and pulse curve is similar to humans, and may potentially be used as a LVAD, RVAD or BIVAD. The device is somewhat large and weighs 85 grams. The auto mode functions to provide physiologic cardiac support. The pump now ready for long term animal experiments.

The LibreCardia ventricular assist system contains a magnetically levitated, centrifugal blood pump, has no valve, seals, or mechanical bearings, and has a two-piece outer shell and impeller/rotor containing the magnet. This system is fully implantable with a small controller/battery and transcutaneous power delivery to the implanted components. The system also uses a mobile charging unit and a handheld patient monitor. Initial animal studies have been conducted in 2 bovine

and 2 ovine. The average pump flow was maintained between 4.5 and 5.5 lpm at 1.5 watts power. Study results showed the device was well tolerated in the juvenile bovine model for up to 7 days, there was stable and reliable hematological and biochemical performance, and the receiver coil did not show tissue damage related to heat injury

A novel disruptive method for the treatment of chronic heart failure called Cardiac MICrocurrent (C-MIC; Berlin Heals) was introduced. The basis of treatment is an increase in cardiomyocyte proliferation rate by microcurrent. The leads used for microcurrent application are a left ventricular epicardial patch and a RV intraventricular coil. The device size is small and is similar to a pacemaker. Acute and chronic experiments in sheep have demonstrated an increase in cardiac output induced by microcurrent therapy and the therapy appears safe. The initial clinical studies in 8 patients are ongoing with results pending.

Challenges in Heart Transplantation

The purpose of the change in the 2018 UNOS heart allocation system are to better stratify the most medical urgent transplants, reflect the increased use of MCS and the prevalence of complications, and to address geographic disparities in access to donors. Modifications have been made to status 1A, 1B and 2 criteria. More information is needed regarding wait list mortality, primary graft dysfunction, survival rates and cost.

There is a learning curve on the use of ECMO as a bridge to heart transplant or implantation of a durable LVAD. The options for patients with INTERMACS profile 1 heart failure are a temporary LVAD (percutaneous or central) with or without a temporary right ventricular assist device (RVAD) as a bridge to decision, VA-ECMO as a bridge to transplant, or a durable LVAD with or without a temporary RVAD as a bridge to decision or transplant. Based on published studies, ECMO as a bridge to transplant is possible with a transplant rate of 75% to 80%, and post-transplant survival is less for ECMO supported patients (70% vs 80% at 1 year). Post-transplant complications of ECMO supported patients include a higher risk of dialysis, stroke and poor functional status.

Are we ready for the widespread use of hepatitis C viremic (HCV) donors in heart transplantation? Approximately 2% of US heart transplants in U.S. between 1994 – 2003 had HCV donors. Recipients of HCV positive donors were more likely to die of viral hepatitis or liver failure (13.7% vs. 0.4%).[28] Multiple direct acting antivirals have been available since 2014 with sustained virologic response >95% depending on HCV genotype and prior treatment exposure. This therapy is well

tolerated and there is a low incidence of drug interactions; no interaction with immunosuppressive medications. In the U.S., these drugs are approved only for treatment of chronic HCV infection. Practical considerations prior to implementation of direct acting antiviral therapy must include collaboration with transplant infectious diseases or hepatology for protocol development, drug dosing, patient follow-up, and infrastructure for insurance preauthorization.

The Molecular Microscope® Diagnostic System (MMDx) is a central diagnostic system that uses microarrays to measure transcript changes in biopsies compared to a Reference Set, using an ensemble of up to 100 predefined machine-learning derived algorithms (classifiers), supervised and unsupervised to define the molecular phenotype and interpret the disease states and their severity. Studies showed the abnormal molecular phenotypes are associated with specifically different hemodynamic profiles and good correlation for acute cellular rejection between pathology and MMDx output, but current classification is inadequate to capture a significant proportion of relevant rejections. The old 1B grade is most likely associated with antibody mediated rejection-like molecular profile. Current ISHLT grading system needs to be revised and an integrated approach including molecular diagnostics and immunopathology may help to improve the diagnostic precision of rejection.

An evaluation of the impact of a pharmacist-led tacrolimus dose adjustment protocol on outcomes in de-novo heart transplant recipients has not revealed significant practice changes. The pharmacist-led standardized tacrolimus dosing protocol did not decrease the time to therapeutic level as compared to standard physician adjustment. If anything, the protocol-based algorithm resulted in a slightly longer time to therapeutic level although no statistical difference was noted, and the sample size was small. The pharmacist led protocol did increase the proportion of time in therapeutic range by 17.9% (equal to 2.5) days (p=0.003). It is too early to reach any conclusion regarding the long-term success of this project. However, the plan is to increase the treatment arm/derivation cohort to approximately 50-60 patients in order to ensure racial, gender, and muscle mass/size diversity. Also, to develop a mobile app for point of care management of tacrolimus dosing based upon pre-defined patient attributes

Challenges in Transplantation and Heart Failure Management

Because cardiac and renal disease are physiologically related and often coexist, the prevalence of combined heart and kidney transplantation (HKTx) has significantly increased over the last few years. It has been suggested that

combined organ allografts modulate the immune system favorably for one or both allografts resulting in successful clinical outcomes. A “safety net” is priority kidney transplantation for those patients who undergo heart transplant alone and who develop persistent renal allograft dialysis or GFR<20 for at least 60 days after the heart alone transplant. There should be aggressive exploration and discussion for living related kidney donors to occur early in the evaluation process for combined heart/kidney to maximize opportunities for evaluation and utilization of such donors; thus, decreasing the impact on the cadaveric renal pool. There is not a recommendation of an age cut off for heart/kidney transplant candidacy or donor candidacy as it could prevent potentially eligible recipients from transplantation and eliminate potentially suitable organs from the pool.

Heart-lung transplant indications include Eisenmenger`s syndrome, primary/secondary pulmonary hypertension, pulmonary atresia/hypoplasia, and advanced cardiopulmonary disease. The number of heart-lung transplants for both adults and pediatrics reported to the ISHLT registry has declined considerably in recent years. The post-transplant morbidity and survival rates have improved over time, while the long-term survival remains poor.

The worldwide donor shortage for allotransplantation is a growing problem. As the number of heart transplant candidates grows, there is not an increase in available donors. The number of transplants in North America are increasing slightly as the number in Europe are declining. Xenotransplantation is a potential solution to the donor shortage; however, achieving long-term survival in pig-to-primate models is challenging. The main challenges are perioperative cardiac xenograft dysfunction, delayed rejection, thrombotic microangiopathy, consumptive coagulopathy, and graft overgrowth. Six-month survival in the baboon model has been achieved, but this must be extended to 1-year. There must be prevention of transspecies infection, and ethical challenges remain for the introduction of xenotransplantation in humans.

Cytomegalovirus (CMV) infection is the most prevalent viral infection after heart transplant and occur in 40% to 60% of recipients. It most likely occurs in the first 6 months after transplant. The different clinical presentations of CMV infection are asymptomatic viremia, non-specific viral syndrome and tissue-invasive disease. CMV infection can exert direct and indirect effects with increased morbidity and mortality. CMV prophylaxis after transplant can consist of virostatic prophylaxis or preemptive therapy. There is no universal consensus on optimal CMV prophylaxis or treatment strategy, or the duration of virostatic therapy. Quantiferon-CMV-guided virostatic prophylaxis is safe and may lead to fewer late CMV infection episodes. CMV-guided approach may lead to a longer virostatic prophylaxis exposure, but is not unavoidably related to higher incidence of leukopenia.

Advances in cancer treatment have improved survival rates of patients with cancer. However, several treatment agents have increased morbidity and mortality due to cardiotoxic effects. Anthracycline is most frequently associated with cardiotoxicity, but new agents can also generate significant left ventricular dysfunction and progress to heart failure. Side effects of this therapy may include myocardial ischemia, hypertension, arrhythmias and heart failure. Endomyocardial biopsy confirms cardiotoxicity diagnosis and is the most sensitive and specific diagnostic tool. Also, cardiac biopsy may identify other causes of cardiac injury and help define further treatment.

Traditionally, ECG is used to triage acute coronary syndrome patients into categories of evolving STEMI, NSTEMI, or no myocardial infarction (MI). The universal definition of MI is based on myocardial injury detected by abnormal serum cardiac biomarkers, primarily cTn, in the setting of acute myocardial ischemia. The definition has undergone four iterations over 18 years – 2000, 2007, 2012, 2018. The universal definition currently provides a structured construct for the differential diagnosis of AMI of various types versus other causes of emergent clinical presentations in order to guide therapeutic decision making. However, illustrative cases have shown the complexity of the application of a universal definition and the contribution of clinicopathological correlation to improving the diagnostic accuracy of the universal definition of MI in clinical practice.

Innovations in Heart Failure Management

Aspirin has been used as a pain reliever, fever depressant, and, more recently, as an antiplatelet agent. It was originally made from willow bark extract but is now made from salicylic acid (sodium calculate). Hippocrates was the first scientist to prescribe bark tree leaves as a pain reliever. A German scientist that lived in Bayer Germany was the first person to stabilize acetylsalicylic acid when he used it to relieve his father's rheumatism in 1897. Today, aspirin is often used in combination with anticoagulants to prevent thrombosis in CV disease. Triple therapy (oral anticoagulant, clopidogrel and aspirin) for percutaneous coronary intervention (PCI) in atrial fibrillation leads to unacceptable bleeding. Possibly, aspirin may be avoided, and a lower oral anticoagulant dose could be used. The most recent guidelines recommend that patients with atrial fibrillation undergoing PCI should use triple therapy for the shortest period that is clinically acceptable (i.e. 1-mo). The balance between bleeding and thrombotic risk must be taken into account.

Specific pharmacological management, mostly focused on neurohormonal suppression, is to improve outcomes in all patients with heart failure and a reduced ejection fraction. No treatment has been shown to convincingly reduce morbidity and mortality in patients with heart failure and a normal ejection fraction. Modifier

genes have been independently associated with the severity and progression of the disease. Several studies have suggested that some patients have a different response to treatment due to underlying genetic differences. Polymorphisms in many genes lead to variability in effectiveness and safety of drugs used in heart failure treatment. Future studies are needed to determine whether pharmacogenetic-guided interventions that encompasses multiple genes and drugs can be implemented clinically to tailor heart failure therapy individually to achieve better clinical outcomes and lower healthcare costs.

Sarcopenia (muscle weakness/loss) plus obesity carries a high mortality in the heart failure population. When compared to non-sarcopenic patients, those with sarcopenia have low body mass index, hemoglobin and albumin, indicative of a poor nutritional state. Obesity and sarcopenia negatively impact the outcomes of patients implanted with a durable LVAD. Weight loss for this population of patients is extremely challenging and compounded by heart failure symptoms of volume overload, shortness of breath, and fatigue resulting in an extremely limited ability for physical activity. For most patients, diet and exercise alone are not enough. Gastric bypass, gastrectomy, banding and biliopancreatic switch are surgical procedures for helping obese patients lose weight. In our studies, patients undergoing LVAD implant in the presence of sarcopenia, have longer lengths of stay in the ICU, and there is a trend towards an increased number of days on mechanical ventilation.

Future Improvements, Challenges and Solutions

Currently, durable MCS has a survival rate approaching that of heart transplant, adverse event rates remain high, quality of life is good but could be better, and growth in use is slowing. The main improvements needed for technology advancement are enhanced hemocompatibility, reduced infection, improved durability, and expanded functionality. Substantial improvements in hemocompatibility have been experienced with the HeartMate 3.[29] Wireless energy transmission for power and control of implanted pumps has the potential to reduce infectious complications.[27] Overall improvements in surgical, medical and outpatient management need refinements to improve outcomes. Lowering anticoagulation levels during long-term support has the potential to reduce bleeding while keeping stroke rates low. Earlier implantation of LVADs and matching technology to patients can help to improve the patient factors influencing outcomes.

The first patient to receive a heart transplant in 1967 survived for only 18 days. By the end of 1968, there had been 102 heart transplants in 50 institutions in 17 countries with a 60% 8-day mortality and mean survival of 29 days. Despite the

unofficial “moratorium” on heart transplantation after 1968, about 12-15 centers around the world continued to pursue both experimental and clinical heart transplantation. Since 1982, well over 100,000 heart transplants have been performed with increasing survival rates over time.[30] The current limitations of transplant are failures due to both over-immunosuppression (malignancy, infection, CKD) and under-immunosuppression (acute/chronic rejection), significant non-fatal morbidities, and the severe supply/demand mismatch. The future of the heart transplant field must include improved immunosuppression and increasing the donation rate and utilization. Improvements in outcomes continue but are incrementally small. Focusing on reducing infections, malignancy and renal failure will likely improve long-term outcomes more than our traditional focus on acute rejection and allograft vasculopathy.

Influenza and bacterial (e.g. pneumococcal) pneumonia (the most common complication of influenza) together are the fifth leading cause of death among Americans over the age of 65 years. Several epidemiological studies have suggested that vaccination against seasonal influenza virus infection significantly reduces the risk of major CV events in patients with acute coronary syndrome or coronary artery disease. The molecular mechanism underlying the cardioprotective effect of the influenza vaccine is unknown. Studies in animals and healthy human volunteers are underway to better understand the cardioprotective mechanisms of the influenza vaccine.

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