VINCENT’S TRADITIONAL SEASONAL SENSE

Again, it’s that time of year. It’s now a tradition for this season to shop to give, celebrate, eat more after Thanksgiving and in the Links review another great masterwork of classical music to rekindle the heart and soul. In regards to stoking the flame, Gustav Mahler supposedly stated “Tradition is not to preserve the ashes but to pass on the flame.” In this final issue of 2016, our inimitable Senior Associate Editor, Roger Evans, delivers an insightful exposé on the definition of a Cardiothoracic Transplant Surgeon – the maestro of heart and lung replacement and transplantation. Such a maestro is at the helm of rather suddenly and deliberately (hmmm is December 7 on my mind?) turning around the state of the sufferer into a more vibrant human with better quality. In keeping with quality, Joshua Mooney gives of us the important message of “Quality and Value in Lung Transplant” transcending beyond the embracing charge of the ISHLT in terms of quality and value for its members and patients. We feel the burning torch of the eagerness of Nikita Desai’s interest in “A Career in Lung Transplantation – A Fellow’s Perspective.” How can the value of such desire be measured for the ISHLT to prove its worthiness than to lay a path for our future and future members other than by reading Nikita’s article?

For added value on the donor side, an ever-increasing need and important update on donor research and potential unmonitored donor adverse effects is reported by David Nelson through an “Update: Institute of Medicine Donor Management Research Study.” Also, Jedediah Lewis of “Organ Preservation Alliance shares with us the initiatives from the White House to reduce the organ shortage in his article on “Taking Aim at Organ Preservation Constraints to Revolutionize Transplant Logistics.” Next, Yasha Kresh, Pablo Huang and Howard Eisen provide us a brilliant, detailed and penetrating explanation with a Shakespearean twist on the protective effects of spiral flow generated by torsional contraction in their summary on the “Functional Architecture of the Heart: Torsional Contraction and Spiral Flow” – “To Swirl or not to Swirl, it’s no longer the question.” Another always reliable Senior Associate Editor, Pam Combs plucks the human emotion yearning to go home, when our VAD patients say, “I just want to go home?” in her brief missive – “The Return Home: VAD patients transitioning home.”

It was the great maestro and composer, Gustav Mahler who was yearning to go home – Vienna - when he was dying from rheumatic heart disease complicated by subacute bacterial endocarditis from Streptococcus viridans. It should be no surprise that Mahler, probably an expert on grieving and suffering through experience from the deaths of his eight brothers, 5 in infancy and three before adulthood; had a morbid obsession with pain, sorrow and death reflected in his music. Not to mention the death of his oldest daughter, named after his insufferable mother, Marie. How he coped with it, hard work and great expressionistic music as summarized in the Editorial’s Corner – “Gustav Mahler: Ahaseurus - The Wandering Jew.” Along with his great compositional works, he left us with, “If a composer could say what he had to say in words he would not bother trying to say it in music.”

Happy Holidays!
IN THE SPOTLIGHT: What Is a Cardiothoracic Transplant Surgeon?

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I frequently recruit transplant surgeons for transplant centers. For the most part, the recruitment of abdominal transplant surgeons is unambiguous, and relatively straightforward. I can easily describe the position for which I’m recruiting. However, when it comes to so-called "cardiothoracic" transplant surgeons, there is considerable confusion. In this regard, when describing transplant surgeons who have something to do with the chest, people often interchangeably use the following terms: cardiac, cardiovascular, thoracic, cardiothoracic, and cardiopulmonary. In my opinion, it’s time to eliminate the ambiguity, and avoid the confusion.

I recently completed a thorough review of the surgical staffing for all adult lung transplant programs in the United States (U.S.). In doing so, I found considerable diversity.

First, let me begin with the obvious. In the United States, a lung transplant surgeon is any qualified and appropriately credentialed surgeon who performs lung transplants at a lung transplant center approved by the United Network for Organ Sharing (UNOS).

Second, going forward, when describing lung transplant surgeons, I believe we should discontinue using the terms “cardiac” and “cardiopulmonary.” They add nothing to the discourse.

Third, based on scope of practice, clinical interests, and practice areas, I’ve concluded that it makes sense to distinguish amongst three categories/types of surgeons performing lung transplants. These categories/types are as follows: (1) cardiovascular surgeons (CVS), (2) thoracic surgeons (TS), and (3) cardiothoracic surgeons (CTS).

Fourth, let me provide the basis for the distinctions I’ve made. This is accomplished in the following table.

Table 1: A Typology of Surgeons Performing Lung Transplants

<table>
<thead>
<tr>
<th>Types of Surgeons Performing Lung Transplants</th>
<th>Procedures the Lung Transplant Surgeon Performs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Transplants</td>
<td>A Wide Array of Cardiovascular Surgical Procedures</td>
</tr>
<tr>
<td>Lung Transplants</td>
<td>A Wide Array of Thoracic Surgical Procedures</td>
</tr>
</tbody>
</table>

...
As is apparent from Table 1, my rationale is unequivocal. There are surgeons performing lung transplants in the U.S. who are essentially cardiovascular surgeons (CVS). Other than lung transplants, they do very little by way of thoracic procedures.

There is a second group of lung transplant surgeons, thoracic surgeons (TS), who not only do lung transplants but, in addition, routinely perform a wide array of thoracic surgical procedures. However, unlike their cardiovascular and cardiothoracic lung transplant surgeon colleagues, they do not do heart transplants, or a wide array of cardiovascular procedures.

Lastly, there is a third group of lung transplant surgeons who are truly cardiothoracic surgeons (CTS). These surgeons do both heart and lung transplants, as well as a wide range of both cardiovascular and thoracic surgical procedures.

There are 197 lung transplant surgeons associated with 60 active adult lung transplant programs in the U.S. Based on my research, I can provide a breakdown on how many lung transplant surgeons fall into each of the categories I have described here. The results are summarized in the following table:

<table>
<thead>
<tr>
<th>Types of Surgeons Performing Lung Transplants</th>
<th>Number</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular Surgeons (CVS)</td>
<td>100</td>
<td>51%</td>
</tr>
<tr>
<td>Thoracic Surgeons (TS)</td>
<td>76</td>
<td>38%</td>
</tr>
<tr>
<td>Cardiothoracic Surgeons (CTS)</td>
<td>21</td>
<td>11%</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td><strong>197</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>

Of the surgeons performing adult lung transplants in the U.S., over half are cardiovascular surgeons, and just over a third are thoracic surgeons. Meanwhile, very few surgeons performing adult lung transplants are truly cardiothoracic surgeons.
I began my research by asking a simple question: what is a cardiothoracic surgeon? I addressed this question in relationship to adult lung transplantation. Given what I found, I feel it is appropriate to ask two additional questions: (1) Who should be doing lung transplants in the first place? (2) Are there variations in patient outcomes based on the type of surgeon who performs lung transplants?

Disclosure statement: The author has no conflicts of interest to disclose.
Quality and Value in Lung Transplant

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During the 2016 ISHLT Annual Meetings President’s Report a call was made to the society to “embrace the role of improving quality and value in the treatment of heart and lung failure.” These terms, quality and value, have permeated healthcare discussions, news, and policy over recent years becoming widely accepted and emphasized metrics for healthcare performance. This development provokes questions for those in the field of thoracic transplant about how we should respond to the evolving focus of quality and value in healthcare delivery.

The lung transplant community has responded to date by acknowledging the resources associated with lung transplant and has worked to understand high resource events, such as the index transplant hospitalization and readmissions. In 2016 alone, the number of publications on resource utilization and readmissions in lung transplant grew exponentially from prior years [1-8]. These recent publications highlight the resources expended in lung transplant and identify factors contributing to high resource use, particularly readmissions. While the identified resource burden is significant so are the life-saving benefits that lung transplant provides to our patients. To ensure that cost saving measures do not adversely influence patient outcomes or inhibit innovation in our field it is imperative that the lung transplant community engages in the charge of measuring and improving quality and value in lung transplant.

A key question is how we should measure quality and value in lung transplant. Individual transplant centers are involved in quality monitoring but are transplant centers monitoring and seeking to improve patient-centered metrics or rather those centered on insurers and governing bodies. Quality metrics such as length of stay and readmissions are used across healthcare but how well do they translate to measuring quality and value in lung transplant. For instance, it remains unclear how preventable readmissions are in lung transplant. Some readmissions may be unavoidable and necessary for ensuring longer-term patient survival or quality. Other readmissions may result from initial surgical complications or breakdowns in transitions from inpatient to outpatient care. Whether we believe they are relevant or not, insurers and governing bodies are embracing these metrics and centers must focus on how to improve these metrics while ensuring the focus remains on the patient not on the number.

One way we can improve quality and value in lung transplant is to embrace the other call from the 2016 ISHLT president’s report to “facilitate knowledge transfer from the high performers.” Lung transplant centers around the world uniformly strive towards the goal of improving the lives of patients with advanced lung disease. Although this fundamental aim is broadly shared, there remains significant variation in how well individual transplant centers achieve it. This variation in care delivery is evident by differences in risk-adjusted survival between transplant centers with similar differences also seen in adjusted readmission rates and transplant admission cost. In short,
there are centers that are providing higher value care, by achieving greater patient survival at lower cost. As we seek to improve value in lung transplant, we need to learn from these high value centers.

Learning from each other may entail positive outlier research where high value centers are identified and their care processes are reviewed. This approach has the potential to understand best center practices or care processes in lung transplant that could be translated to other programs. For example, ambulatory extracorporeal membrane oxygenation (compared to non-ambulatory) has shown to be a cost-savings way to bridge patients to lung transplant [2]. Identification of similar care practices has the potential to improve patient outcomes, quality, and value. Whether identified high value center practices could be generalizable and transferable to other centers is uncertain, and therefore testing of transplant care processes across multiple centers may be necessary.

Notably, the busyness of a transplant center is associated with value, as higher center volume is generally associated with better survival, lower readmissions, and lower cost.[6] This speaks to the importance of directly learned experience in lung transplant outcomes, quality, and value. Some countries already only provide care at regionalized transplant centers, however this approach may not be applicable to all countries and healthcare systems. Therefore, we are faced with the arduous task of improving quality and value in lung transplant through working together and facilitating knowledge transfer and education of high value care process that improve patient outcomes and lower cost. The value of lung transplant will ultimately be determined by how lung transplant is practiced which is something we are responsible for. Therefore, let us lead the way in improving lung transplant quality and value.

Disclosure statement: The author has no conflicts of interest to disclose.

References:
As I entered my fellowship, eager to immerse myself in the knowledge of pulmonary physiology, critical care, and advanced lung disease, I was struck by the unexpected and often frustrating role of managing my patients’ expectations. Rarely did a patient walk into my Monday afternoon clinic with a complaint I could definitively cure. Most of the time I was counseling patients on their new diagnosis of a chronic, irreversible disease with difficult to manage symptoms. I found myself wishing I could do more, and that my paltry offerings inhalers, influenza vaccines, and pulmonary rehabilitation felt surprisingly inadequate. It wasn’t until my rotation in lung transplantation that I was able to offer hope, however slim, to the patient with end stage lung disease. Suddenly I saw that patients who were substantially limited could finally be able to do things we take for granted: grocery shopping, attending a baseball game, traveling to visit family.

As a trainee, lung transplantation has allowed me to care for a patient using the same complex medical decision making that drew me to the intensive care unit in the first place. Managing chronic medical illness in conjunction with the evolving donor-recipient biologic model is both intellectually stimulating and clinically rewarding. Furthermore, to see a patient and their family through lung transplantation is to be given the opportunity to see the best in people. From intensive pre-transplant preparation, to rehabilitation, relocation, education, long hospital days, and countless follow up appointments in the post-transplant phase, patients and their families have shown unrelenting perseverance, sacrifice, dedication, and true grit.

As rewarding as it is to care for patients seeking lung transplantation, it is equally exciting to pioneer scientific innovation. In the past two decades, we’ve made significant strides in the realm of immunology and biopharmaceutics. Targeted genetic therapy has improved lung function in patients with Cystic Fibrosis, a disease which affects 30,000 people in the United States. The CF experience has shown that specifically addressing the intracellular trafficking of a misfolded protein can lead to a dramatic change in lung function. This raises optimism for lung transplantation, particularly if we can figure out the key intracellular signals that lead to luminal obliteration of the terminal airway. While the pathogenesis of Obliterative Bronchiolitis remains an enigma, this is an engineering problem to be solved, rather than an insurmountable hurdle.

By comparison, Chronic Obstructive Pulmonary Disease affects over 15 million people in the United States and the scientific community has made limited strides in improving mortality and length of life. One glance at a CT Scan of a patient with bullous emphysema is enough to convince even a lay person that pharmaceutical options are limited. Over the past three decades we’ve made gains in our ability to transplant older, sicker patients, and broaden our donor acceptability criteria; however, we continue to be limited by donor availability. Xenotransplantation could be one
potential solution to this problem. It is this ability to address the needs of millions that drives us forward.

A trainee considering a career in lung transplantation is at the forefront of a field where there are more questions than answers, room for pharmaceutical and technological development, and a patient population eager for treatment options. Advancements in clinical, genetic, and environmental factors give promise to one day transitioning from center regulated transplant protocols to tailored patient specific therapy. It is my generation’s duty to apply advancements in lung transplantation to other aspects of pulmonary disease. There has never been a more exciting time to enter the field of lung transplantation.

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Highlights of the European Society for Immunodeficiencies Meeting

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The 17th Biennial Meeting of the European Society for Immunodeficiencies (ESID) was held in Barcelona, Spain on 21 – 24 September 2016. Basic and clinical research in the field of primary immunodeficiencies (PID) was covered at this year’s meeting from diagnostic immunology, to genetics and the immunobiology of immunodeficiency, immune dysregulation and inflammation. These topics together with other advances in the area of tolerance induction and new insights into cellular therapies were discussed through distinct keynote lectures, symposia, educational workshops and meet-the-professor sessions.

Thymic function can be determined by T-cell receptor excision circle (TREC) analysis. A perspective on newborn screening in the United States was presented by Jennifer Puck, from the Department of Pediatrics at the University of California, San Francisco School of Medicine. The TREC test for newborn screening of severe T-cell deficiencies was approved for severe combined immunodeficiencies screening by the US Food and Drug Administration (FDA) in 2014.

Targeted therapies have emerged as new treatment options for several diseases including cancer, autoimmune disorders and transplantation. Ibrutinib is a protein-tyrosine kinase inhibitor of Bruton's tyrosine kinase (Btk), a kinase of the B-cell receptor signaling pathway. Ibrutinib is FDA-approved for the treatment of chronic lymphocytic leukemia (CLL), mantle cell lymphoma and Waldenström’s macroglobulinemia. BTK-inhibitors are an example among drugs emanating from research on PID. Edvard Smith from the Karolinska Institut in Sweden, presented data on the effects ibrutinib in CLL patients including the induction of decreased levels of CCL3, CCL4 and CD16-positive 6-sulfo LacNAc (SLAN) positive monocytes.

Complement C3 hypocomplementemia is frequent after heart transplantation. Interestingly, Anais Jimenez-Reinoso from the Complutense University, Madrid, Spain, demonstrated that in vivo naïve B cell differentiation to memory B cells was selectively impaired in both primary and secondary extracellular C3 deficiency.

It is important to remember that antibody deficiency can be present in patients with normal serum IgG concentration. B. Lopez from the Lille University, France, presented data of patients with specific polysaccharide antibody deficiency, defines as an impaired antibody response to polysaccharide antigens and normal serum IgG/A/M and IgG subclass levels.

Jose Lucena from the Hospital Virgen del Rocio, Seville, Spain, reported on immunological characteristics in patients with selective IgM deficiency. Lower percentages of non-switched memory B-cells were observed in these patients.
Gain-of-function mutations refer to a mutation that confers new or enhanced activity on a protein. It has been shown recently that some primary antibody deficiencies are caused by hyperactivation of the PI3K signaling pathway, as gain-of-function mutations. Maria Martínez from the Gran Canaria Hospital, Spain, suggested that gain of function mutations in PIK3R1 can be found in patients with a narrow clinical phenotype (i.e. with only respiratory infections) suggesting that early diagnosis and careful analysis of B and T-cells followed by genetic analysis is necessary in these cases.

To establish whether hypogammaglobulinemia is due to a latent primary antibody deficiency, that becomes manifest after Rituximab therapy, or to Rituximab treatment that causes a persistent B cell defect, is a difficult task in some cases. Viviana Moschese from the Tor Vergata University, Rome, Italy, suggested the need of an extensive immunological characterization before and after Rituximab therapy.

Interindividual variations of immunoglobulin constant heavy G chain genes are identified by alternative genetic markers of IgG3, IgG1 and IgG2. They express structurally and functionally innate IgG molecules and B cells. The alternative innate IgG subclass proteins are unique entities and have different structures and functions. New individual innate IgG subclass variants were described by Vivi-Anne Oxelius from the Lund University in Sweden. The alternative IGHG subclass genes respond differently to bacterial antigens, virus and allergens, having impact on diseases and phenotypes of diseases.

A characterization of antibodies against 24 pathogens was performed by N. Marzo et al from the Bioscience Industrial Group Grifols, Barcelone, Spain, in 12 commercial intravenous immunoglobulin (IVIG) brands obtained from pooled plasma of different geographic areas. Overall, IVIG products showed a high level of reactivity against the studied pathogens, regardless the geographical origin (i.e. measles, diphtheria, tetanus, Epstein-Barr and CMV). However, in countries from North America and Pacific, a cluster of relatively higher titers for different pathogens including Parainfluenza, Influenza B, Epstein-Barr, Varicella and Measles, were observed. IVIG products form Asiatic countries were in the lower titer range for the same pathogens. In India, high antibody levels against Dengue, Chikungunya, West Nile Virus, Hepatitis A and E were observed. The authors suggested that vaccination programs and incidence of pathogens might have an impact on IVIG antibody titers of a particular region.

This year's Nobel Laureate Yoshinori Ohsumi discovered mechanisms underlying autophagy, a process for degrading and recycling cellular components. Autophagy, is also known to contribute to cell intrinsic immunity against viral infection. An impairment of herpes simplex virus 1-induced selective autophagy was described by Liyana Ahmad from the Imperial College London, Department of Virology, London, United Kingdom, in patients with herpes simplex encephalitis.

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Update: IOM Donor Management Research Study

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As previously reported in Links, two HRSA funded donor management research consensus conferences were held in Crystal City, November 2014 and Philadelphia, May 2015 to define barriers to donor management research and explore their possible solutions. The conferences recommended that a national oversight board be developed to assess ethical and scientific merit and provide safety monitoring for these studies and observed that the existing network of regulations which safeguards us from human research abuse is a misfit for donor related research in the complex context of organ allocation. In response to efforts of the consensus conferences and others the Institute of Medicine (now National Academy Medicine) has initiated a study to “examine the ethical, policy, regulatory, and operational issues relevant to the conduct of research involving deceased organ donors...that aims to increase the quality and quantity of donated organs”.

A criteria for IOM committee membership for this project was that the member not be currently active in transplantation or procurement. This criteria was established to avoid bias or conflict of interest in the work of the committee. However, input from the transplant and procurement communities is invited, specifically sought as needed, and actively engaged in scheduled public sessions of the committee with invited speakers from these communities. The first of these public sessions occurred at the National Academy of Sciences building in Washington DC on September 29 when representatives of the sponsoring organizations shared their perspectives and hopes with the committee.

The IOM committee has 12 members, 7 of whom are physicians, two are attorneys and 2 are former transplanters. Membership includes representation from the OPO community, pediatrics, one of the physicians is a liver transplant recipient, another physician is former Surgeon General of United States and there is significant representation from the ethics community. The two former transplanters are abdominal surgeon William Marks from Seattle and cardiologist Jim Young from the Cleveland clinic.

The chair of the committee is James Childress PhD who is emeritus Prof. of Ethics and Religious Studies at the University of Virginia. He is author of several textbooks on biomedical ethics, former chair of the National Task Force on Organ Transplantation, has served on the UNOS board of directors and the UNOS ethics committee. He was a member of the presidentially appointed National Bioethics Advisory Commission, he is a member of the National Academy of Medicine and has chaired several studies by the Academies.

Academies staff Study Directors are Cathy Liverman and Sarah Domnitz. The study sponsors are the Laura and John Arnold Foundation, American Association for the Study of Liver Diseases, American Society of Transplant Surgeons, American Society of Transplantation, The Association of
Organ Procurement Organizations, the Gift of Life Donor Program, National Kidney Foundation, National Heart Lung and Blood Institute, the National Institute of Allergy and Infectious Diseases, the National Institute of Diabetes and Digestive and Kidney Diseases, and the Transplantation Society. Additional agencies and organizations may potentially later co-sponsor the project.

The next public session at the National Academy is December 15 when the following 6 panel presentations will occur: 1) impact of research on organ donation recovery and transplantation; 2) barriers, opportunities, and lessons learned from organ donor intervention research; 3) future approaches to organ donor intervention research study design; 4) federal perspectives on organ donor intervention research; 5) public awareness and public trust; and 6) ethical and legal considerations. Speakers will include Dave Klassen from UNOS, Bert Kasiski of SRTR, Jim Gleason of TRIO and former UNOS Pres. Tim Pruett.

The ISHLT is providing the IOM project with outcome metrics developed by the Heart and Lung Scientific Councils intended to address the potential for unmonitored adverse effects of donor research occurring to organs not primarily targeted by a study (e.g. a kidney study having unexpected cardiac or pulmonary consequences). The metrics were a charge to professional transplant societies by the HRSA’s Donor Management Task Force in 2011.

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Taking Aim at Organ Preservation Constraints to Revolutionize Transplant Logistics

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Last June, the White House convened the first Organ Summit, bringing together many stakeholder organizations across transplantation to discuss ways to reduce the organ shortage [1]. The Organ Summit heavily emphasized the promise of research and development to provide solutions for patients on the transplant waitlist, unveiling new initiatives aimed at organ preservation, tissue engineering, donor management, bioartificial organs, and reconditioning of marginal organs, among other topics [2].

Among the initiatives announced by the White House was the upcoming Summit on Organ Banking through Converging Technologies, organized by the Organ Preservation Alliance [2]. The Summit is part of a growing research effort aimed at dramatically increasing preservation time and quality for transplant organs, combining advances in ex vivo perfusion, cryopreservation, hibernation and related areas that have occurred in recent years [3–5]. This effort has been spearheaded by an interdisciplinary coalition of transplant professionals, researchers and engineers; the consortium supporting it includes entities as varied as the American Society of Mechanical Engineers, Society for Cryobiology, and Association of Organ Procurement Organizations [2].

The technologies being pursued could have a profound impact on thoracic transplantation. Today utilization rates for donor hearts in the U.S. are roughly 30%, and roughly half these grafts have been rejected after 10 years [6,7]. Meanwhile lung offers are accepted only 20% of the time, and almost 3/4 of transplants have been rejected within a decade [6,7]. These numbers result from many factors, but they’re fueled largely by logistical constraints that can be addressed by achieving new preservation capabilities.

Preservation advances could create new possibilities for organ assessment prior to transplantation, allowing utilization of more hearts and lungs without adding risk to patients. They could provide windows for gene therapy, immunomodulation and immune tolerance induction, as well as new approaches to reanimate and repair marginal organs. Extending preservation times would enable donor-recipient matching over longer distances and could allow new methods to screen for transmissible diseases and malignancies. And it would add more flexibility to transplant surgery, lowering costs and make the surgical team’s lives easier.

Like with any platform technology, organ preservation is likely to lead to new approaches that would be unthinkable under today’s circumstances. For instance, cryopreserving and banking organs has been suggested as a way to tap unused ‘borderline’ organs (studies have suggested that most hearts may fit into this category) as a backup supply in case of primary graft dysfunction. Preservation advances can also accelerate progress toward other technologies that are
on the horizon. It could also make xenotransplantation research a much more attractive investment, by allowing access to the same manufacturing capabilities (maintaining an inventory, quality control, global distribution, etc.) that many other industries enjoy.

This reasoning – make commercialization of a technology that can address the organ shortage more feasible, and research investment will follow – was reflected at the White House Organ Summit, in the form of a $160 million solicitation for an Advanced Tissue Biomanufacturing institute. The institute will focus on developing technologies and make tissue engineering clinically and commercially more feasible; the announcement and solicitation emphasized tissue preservation as a major component [2,8].

Researchers and clinicians seeking to capture these benefits have put together a compelling vision for preservation capabilities of the 21st century and have begun to chart the research path to get to us there at recent events such as the first global Organ Banking Summit, [9] an NSF-funded roadmapping workshop, [10] and a White House Roundtable on Organ Banking and Bioengineering. By building on the last decade’s revolution in ex vivo perfusion and combining it with cryopreservation methods that have worked well for cells, human embryos, simple tissues, and even whole organisms that can enter ‘suspended animation’ in nature, a focused research effort could achieve flexible infrastructure for transplantation in which an organ can preserved under conditions that vary according to need – allowing for unrestrained transport, new methods for assessment and repair (including at specialized facilities), and, when needed, even extended storage of organs.

Achieving these technologies will be no easy feat, and no small-scale effort either. On the contrary, organ preservation is an exceptionally interdisciplinary challenge: the quintessential “convergence technology” [11,12]. Which is why the upcoming Summit will bring together organ preservation researchers and other members of the transplant community with scientists and engineers from a diverse set of surrounding fields, such as nanotechnology, imaging, metabolomics, that were identified during the NSF roadmapping process [10].

Members of the ISHLT community from all backgrounds are welcome. Their expertise will be needed to push this effort forward, for the benefit of the transplant community and the hundreds of thousands of patients worldwide still waiting for a new organ.

To learn more about the Summit, visit obs2017.org. To learn more about the Organ Preservation Alliance, visit organpreservationalliance.org or contact jedd@organpreservationalliance.org

Disclosure statement: The author has no conflicts of interest to disclose.

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Functional Architecture of the Heart: Torsional Contraction and Spiral Flow

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Most, if not all, treatment modalities to correct and/or replace cardiac structural abnormalities are rooted in representing the heart as a pressure generating source for propelling blood circulation. Not until very recently has the helical structural arrangement of the cardiac muscle and the torsional dynamics (twisting and untwisting) of the ventricles during ejection and relaxation gained wider recognition and clinical impact. Much of this occurred in the past decade with the advent of sophisticated non-invasive dynamic 3-D imaging (i.e., Echo, MRI) of the blood-flow velocity patterns, exhibiting spiraling / vortical streamlines emanating from the ventricles. The specific molecular signaling pathways and significance (adaptation, pathogenesis) related to the more complex, momentum imparted, spiral flow in normal physiology and its alteration in heart failure leading to the onset of vascular pathophysiological states (atherosclerosis, thrombosis) needs to be fully elucidated.

Spiral blood flow, capable of organizing multi-directional streams, has been associated with flow stability (decreased turbulence), cardiovascular disease process deterrence, improved lumen-wall oxygen transport, and washout effects by reducing blood element adhesion to vessel walls [1, 2, 3, 4]. The phases of the cardiac cycle produce variable helical content in the flow, which may modulate plaque formation by regulating the wall shear stress (WSS) mediated mechanotransduction signaling pathways of endothelial cells [4, 5]. Shear stress operates on a number of spatio-temporal scales known to regulate focal endothelial gene expression; it can signal WSS-induced atheromatous and/or thrombotic susceptibility due to flow disturbances resulting from physiological branching/curvature, stenosis (remodeling) and presence of intravascular devices [6, 7].

Remarkably, despite the increasing recognition that spiral flow may play a pivotal role in preserving endothelial homeostasis via the regulation of laterally directed forces and the normalization of WSS gradients, very few existing implantable cardiovascular devices (total artificial heart, ventricular assist device, grafts, stents) incorporate helical features into their design considerations for fluid dynamic optimization. Mechanical circulatory support (MCS), for example, is increasingly being used for long-term hemodynamic augmentation in heart failure patients. Re-establishing native spiral fluid flow structures may improve device functional patient compatibility. In its current form, mechanical heart valve replacements continue to generate flow disturbances - such as induced...
jetting, flow separation, and shear stress gradient increase - leading to platelet activation and blood trauma [8].

Intriguingly, the incorporation of helical design forms integrated into bypass grafts was shown to enhance flow uniformity at anastomoses, absence of noted recirculation regions, decrease in platelet aggregation, and mixing of low-high momentum fluid within vessels [9]. Stent designs containing helical features were associated with reduced neointimal hyperplasia in stented arteries, compared to conventional straight stents [10]. In our ongoing studies, we have been able to demonstrate that induced spiral flow was associated with diminished fluid jet dynamic pressure. The reduction in fluid jet force impact is particularly important in ventricular assist device outflow cannula designs, and an important consideration in general anastomoses.

**Translational Perspective:**

The precarious (unintended) scrambling of spiral flow that may be caused by bileaflet mechanical valves, due to their inherent design criteria, has not been examined as a source for disrupting physiologically protective conditions attributable to spiral flow. In our preliminary studies, the preservation/propagation of generated spiral flow has been demonstrated to be valve-specific; the valve orifice geometry and leaflets play a crucial role in flow-pattern (de-)modulation.

The incorporation of spiral flow into the outflow track of mechanical circulatory systems and devices may contribute materially to the reduction of aneurysm-promoting wall forces (vascular lumen mechanical integrity) and increase transport efficiency across the cannula – aorta interface, optimize device energy demand, and attenuate the degree of aortic insufficiency. The impetus remains for designing continuous-flow mechanical circulatory assist devices and other interventional therapies (e.g., macro/micro patterned helical stents) that incorporate the proven beneficial attributes of spiral flow dynamics. The more biologically-inspired designs may provide opportunities for minimizing blood element damage (e.g. vWF uncoiling, RBC lysing, platelet activation), facilitating more precise/safer anticoagulation therapies.

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References:


The Return Home: VAD Patients Transitioning Home

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How many times have we heard a VAD patient say “I just want to go home?” And we typically respond with an objective, well-scripted response as why the patient can’t go home “now” but that indeed the team’s plan aligns with their request. The key to the patient/caregivers’ adjustment of living at home with the VAD involves processes, communication, extensive planning to name a few, but what is the return home experience like for the VAD patient?

Though the VAD team may celebrate the newly implanted VAD patient’s discharge home, the work is only beginning.

In general, the VAD team’s perspective regarding the VAD patient’s outpatient life consists of clinic visits, telephonic triage, support meetings, and facetime monitoring. The patient’s transition home involves a noticeable change in daily routine and resumption of activities. The patient arrives home with multiple VAD components, dressing supplies, and education manuals to name a few. Additionally, friends and family may look at the patient differently, may be afraid to touch the patient for example. To the converse, friends and family may think the patient is ready to do everything, that the patient should be immediately “fixed.” An array of emotions exist with our patients returning home. A diary/journal may help the patient express their emotions. The team’s Social Worker may plan to visit the newly implanted patients first time to clinic to assess their transition home. The VAD Coordinator may observe cues that indicate a difficult return home. This assessment should be at a high level immediately after discharge and should be discussed at the first clinic visit. Though home is the ultimate goal, assuring the transition is smooth as possible is crucial to enhance positive outcomes and a better quality-of-life.

There is no place like home, but it is important to remember that the patient returns home with a different outlook, physical status and daily life. Pay heed to this transition, offer time for the patient to discuss any concerns and offer problem solving to address any obstacles that may exist. For the return home is just the beginning.

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EDITOR’S CORNER: Gustav Mahler: Ahaseurus – The Wandering Jew

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This is the sixth consecutive December in which the Links steers our attention to Great Musical Composers and how they enhance our cultural and creative side of what we do for and in the ISHLT. (see 2011, 2012, 2013, 2014, and 2015. From Dvorak, Beethoven, and Mozart to Berlioz and Tchaikovsky, we turn to a summary on the life and works of Gustav Mahler encompassing a personal expression of his inner world characterized by a sense of alienation and loneliness. This sense relates to our theme of Volume 8 as we gain a better handle of what our patients deal with while suffering from a failing heart and/or failing lungs. Mahler was once quoted – “The symphony must be like a world: it should contain everything.” In his symphonies and song cycles, Gustav built a complete world, involving every kind of human experience, from childlike innocence and wonder to anguish and despair. To achieve this, he wrote music for a huge orchestra, sometimes with voices added. He pushed musical form to the limit with exciting new harmonies. Listening to his music can be overwhelming and rewarding. His most famous work, Symphony No. 8 was known as “The Symphony of a Thousand” due to the large orchestra and choir it requires, this piece includes church text and a section from Goethe’s Faust.

He was born to Jewish parents in Kalischt, Bohemia on July 7, 1860 in what was then part of the Austrian Empire and today, the Czech Republic. Like many emancipated Jews, the Mahler family considered themselves as Western European Jews and spoke German at home, not Yiddish. His life centered on isolation and alienation in part due to a brutal father and the racial tensions of outright anti-Semitic hostility in Austria including the Viennese Press. Mahler wrote, “I am thrice homeless, as a Bohemian in Austria, as an Austrian among Germans, as a Jew throughout the world, everywhere an intruder, never welcomed.” As a young man, Mahler identified himself as Ahaseurus, the Wandering Jew. His intense suffering from anti-Semitism extended beyond his life insomuch after his death in 1911, his music was condemned and banned by the Nazis as being both degenerate and Jewish. His music went largely unnoticed for nearly 50 years.

As a defense against this abuse, hostility and loneliness, Mahler retreated into a fantasy world enabling him to create extraordinary and fantastic music-scapes. He became entranced by music which began with an unbending devotion to the piano and yearning to compose. He developed morbid tendencies resulting in bizarre juxtapositions of tragedy, humor, despair, passion and rage that disappeared as quickly as they suddenly and explosively erupted in his music. Such expressive themes resulted in great orchestral pieces distinguishing him as a father of musical expressionism, the actual recipe which influenced and continues to influence many theatrical composers today. The environment that shaped Mahler’s soul, his musical and emotional landscapes were fortunately united by him with tortured emotions stemming from his childhood into rich and original music.
Take particular note of his first Symphony, Movement 3, – and notice the tune of “Are you sleeping?”, “Frere Jacques,” or “Bruder Jakob” named by him, the Funeral March. Mahler considered this tune quite morbid for children and provides an example of his obsession with death and the ritual sadness of a funeral march followed by the joy of dance. This joyous dance theme may have influenced Jerry Bock to compose the tune – “If I were a Rich Man” and the instrumental “Bottle Dance” from Fiddler on the Roof in 1964.

In 1875, Mahler studied music at the Vienna Conservatory and was regarded a marvel. He was influenced by Richard Wagner and listened in person to Wagner and Brahms conducting and Liszt and Anton Rubinstein playing the piano. By 1880, Mahler was not a rich man. Tired of living in constant need of money and knowing that composers made money by conducting, he turned to conducting even though he never conducted. He began his career as a conductor at a small theater in upper Austria and immediately found his calling. He became an exceptional conductor rising up from the Landestheatre at Laibach, the Stadttheatre in Olmultz (Moravia), Landestheatre in Prague and Neues Stadttheatre in Leipzig to an appointment as music director and first conductor of the Royal Hungarian Opera in Budapest and assumed the post of conductor at the Hamburg Stadttheatre, one of the oldest and most prestigious opera theater in Europe. At his height, he would conduct nineteen different operas a month with an uncompromising and tireless style. He was a merciless crusader against mediocrity with extraordinary attention to detail. All of these elements would make up his later compositions. In 1897, Mahler applied for the position as conductor of the Vienna Opera. In February that same year, he converted to Catholicism, not for religious reasons, but because it was the only way he could secure the position as conductor and music director in Vienna. It was ten years later that the anti-Semitic Viennese press drove him out of Vienna.

In November 1901, Mahler, at the peak of his career as a conductor in Vienna met and married Alma Schindler. He experienced the best years of his life from 1902 – 1907 when he and Alma had a family and a summerhouse where he could compose. His Symphony No. 5 was a superb example of expressionist art movement with progressive emotional states of the grieving process. In movement 2 of Symphony No. 5 he provided the mourners of death time to reflect on the loss of a love one filling them with rage. Then near the end of this movement is a glimpse of joy that “all things will pass.”

1907 was the beginning of the End for Mahler with three morbid blows to his psyche: 1/ his forced resignation from the Royal Viennese Opera; 2/ the death of his elder daughter, Maria; and 3/ the diagnosis of his diseased heart. He had been the music director of the Royal Vienna Opera for 10 years when he was decidedly exhausted and disgusted with the ungrateful public who booed him from the promenade seats behind the orchestra. He was weary from the ongoing battle with careless and mediocre singers and was ultimately humiliated when his request for a new contract was publicly turned down. And of course the anti-Semitism of the Viennese press didn’t help matters. After living in one place for a decade, he once again became Ahaseurus, “the Wandering Jew.”
Upon return to their Summer home in June, 1907, Gustav’s daughters fell ill from a combination of scarlet fever and diphtheria. His younger daughter, Anna recovered, but his older and favorite daughter, Marie, required a tracheostomy with lingering suffering for two weeks before her death. However, the pain of her illness was most unbearable for Mahler. Upon Marie’s death, Mahler was diagnosed with a serious heart condition with valvular abnormalities – but his doctors at the time assumed the worse and advised him not to engage in any exercise or sports. Mahler had been an avid swimmer and vigorous hiker through the mountains. Reportedly, Mahler never spoke about the death of his daughter, and he forbade his wife Alma from wearing mourning clothes. He was able to cope by reading and composing voraciously.

Afterwards, at age 47, Mahler became a wanderer again and landed a four-year contract with New York’s Metropolitan Opera where he conducted three months a season. After each season in New York, he would return to the Austrian countryside to compose his final works. He composed Das Lied von der Erde and his 9th and 10th symphonies. In the summer of 1908, he slaved over the melancholy poems of Das Lied which allowed him to deal with the grief and anxiety over the death of Marie and his constant fear of his own heart ailment. Interestingly, Mahler had intended to call Das Lied von der Erde his 9th Symphony, but he took the curse of the ninth symphony very seriously. The superstition that Beethoven, Schubert, Bruckner and Dvorak met their death was the culminating blow to what happened to him only preceded by the death of Marie and his own heart condition. Mahler wrote, “At one blow, I have simply lost all of the clarity and quietude I ever achieved. Now I’m at the end of my life, again a beginner.” He decided not to tempt fate and named his 9th Symphony, Das Lied von der Erde. His Symphony No. 9, actually his tenth was his last completed symphony.

The six songs of Das Lied came from the texts by Hans Bethge’s translation of Chinese poems. Mahler arranged the songs to create progressive drama about loss, grief, memory, disintegration and transfiguration, sort of an autobiography. His Symphony No. 9 (actually the tenth) was filled with premonitions and contemplations of his own death. The introduction of the first movement of Symphony No. 9 depicts his own heartbeat followed by a “fluttering sound” of his leaking valves. He was then resigned to his heart disease with a fatal heart attack in this first movement. His music was now about resignation and acceptance. Mahler was composing Symphony No. 10 which remained incomplete when he died. He had returned to New York for his fourth and final season in 1910. He was tired and developed a sore throat. By February, 2011, his sore throat lingered when he started spiking fevers up to 104 degrees. He was examined by Joseph Fraenkel and reportedly by Emanuel Libman in New York. He was febrile, pale, and clubbed. A loud murmur, splenomegaly and conjunctival petechiae were described. Streptococcus viridans was cultured from his blood. He was among the first to have an accurate microbiological diagnosis of subacute bacterial endocarditis. At that time, antibiotics were unavailable and there was no cure. He wished to die in Vienna to be buried with his daughter. He traveled by ship from New York to Cherbourg, then by train to Paris. Then, he took the Orient Express to Vienna where he was placed under the care of Franz Chvostek at the Loewe sanatorium. He was prescribed an experimental antistreptococcal immune preparation along with oxygen, caffeine, digitalis and radium compresses for his acutely swollen joints. He died on May 18, 1911 in Vienna, his last word was “Mozart.”
The New York Times called Gustav Mahler, “one of the towering musical figures of his day.” With a compositional career that began when he was six and to its end, his music focused on the lonely isolated individual attempting to cope with romantic rejection, the struggle between hope and despair, the questions of death and redemption, and the grieving process. Mahler also had an exceptional career as a conductor. He was the first all-powerful maestro and the model for many other famous conductors of the 20th century.

Mahler believed that sorrow “made the man.” He praised it as the defining element of life and believed that sorrow endowed a person with emotional richness and depth.

Disclosure statement: The author has no conflicts of interest to disclose.

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