THIS MONTH'S FOCUS:
PEDIATRIC TRANSPLANTATION
HEART FAILURE & TRANSPLANTATION

In the Spotlight: ISHLT's Guide to Nice, France

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With our Annual Meeting planned in a location as beautiful as Nice, we know there is much to consider outside the walls of The Acropolis. With this in mind, we have compiled a tourist's guide to all the top attractions in Nice that we will break down to share in each new issue of the Links Newsletter.

This month's focus will be on Monuments and Churches. Though both are abundant among the rich culture and history of Nice, we have chosen to highlight a few more notable examples.

Monuments and Churches

http://en.nicetourisme.com/monuments-and-churches

- **Le Fort du Mont-Alban** - Built on a hilltop 222 meters above sea level, the Fort is a massive 16th century structure offering exceptional panoramic views stretching from Italy (tip of Bordighera), Cap d'Ail, St Jean Cap Ferrat and the Bay of Angels, to Garoupe Antibes and, on a clear day, all the way to Corsica.
- **Le Negresco** - Built on the shores of the famous Baie des Anges in 1912 by Niermans for the Romanian Henri Negresco, this Belle-Époque landmark is the only museum and luxury hotel in Nice. A listed historic building since 2003, it houses collections retracing five centuries of art history. The 121 rooms and 24 suites each have their own decoration. Recently promoted to the 5-star category, it is reputedly one of the world's finest hotels.
- **La Place Rossetti** - Surrounded by Italian-style architecture of red and yellow townhouses and situated in the center of Nice's old town, Place Rossetti is a charming square featuring a small stone fountain and the lovely baroque Cathédrale Sainte-Réparate. The square and its many sidewalk cafés attract a bustling daytime crowd of residents, families, and travelers eager for a bit of refreshment and relaxation.

- **La Tour Bellanda** - Built on the foundations of a defensive structure razed to the ground during the French occupation under King Louis XIV, Tour Bellanda was home to the great 19th-century French composer Hector Berlioz while he was writing the King Lear Overture. Today, it is adorned with ceramic mosaics of ancient Greek motifs, and the terrace offers a splendid panorama over the city and its surroundings.
- **Cathedrale Sainte-Reparate -** This church, which became a Cathedral in the 16th century, is the largest sanctuary in Old Nice. Inspired by early Baroque architectural models from Rome, the structure has a basilical layout; with a triple nave and a transept. The decoration of the side chapels and choir is particularly sumptuous and the interior reflects the influence of Saint Peter's of Rome.
- **Chapelle de la Misericorde -** Built after 1740 and designed by the famous architect Bernardo Vittone, the chapel has an elliptical nave, with semicircular side chapels. The wealth of the decoration inside, the originality of its volumes and the murals by Bistolfi make this a genuine gem of Baroque art and an exceptionally rich example of the area's architecture.
- **Basilique Notre-Dame -** The largest church in Nice and the first modern religious structure, the basilica of Notre-Dame was built after Nice became French (1864-1868). Inspired by the Cathedral of Angers with its two square towers, it is adorned with 19th-century stained-glass windows and a sumptuous rose window with scenes of the Assumption.

Cardiac Recovery: The Best of Times, the Worst of Times

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A Tale of Two Cities comes to mind when I think of 2 recent patients and their potential for cardiac recovery. Both teenagers presented acutely with dilated cardiomyopathy and decompensated heart failure. Both patients were scheduled for elective VAD implant due to progressive deterioration on intravenous inotrope support. "Ana" received an acceptable donor organ 24 hours prior to the scheduled VAD implant. Ana's graft functioned well initially. "Jonathon" deteriorated precipitously prior to the elective VAD and suffered neurologic injury while undergoing VAD implant emergently.

Their stories continue. Ana developed antibody-mediated rejection due to a non-HLA antibody. She died 6 months post-transplant from systemic Aspergillus, a result of aggressive immune suppression to treat the rejection. Perhaps VAD implant prior to heart transplant and a watchful eye for ventricular recovery would have benefited Ana. Jonathon had myocardial recovery despite a diagnosis of familial dilated cardiomyopathy. His VAD was explanted 6 months after initial implant. Unfortunately, the heart failure recurred, and he suffered an additional neurologic insult at the time of the recurrence. Both stories illustrate "the best of times, the worst of times". Both stories leave questions regarding myocardial recovery.

Much has been written about myocardial recovery in the adult literature (1-7). There is comparatively sparse literature pertaining to recovery in pediatric heart failure (8-9). How does medical therapy or device therapy impact myocardial recovery in pediatric heart failure? Additionally, is recovery simply a matter of allowing time for recovery to occur in select children? We are likely to identify and treat myocardial insults that lead to heart failure, such as neurohormonal activation, inflammation, hemodynamic derangements such as pressure or volume overload, toxic insults, or myocyte energy impairment. However, identifying who will recover myocardial function long-term or permanently remains an enormous challenge. Are there biochemical markers we can use to predict recovery at diagnosis and/or during medical or device therapy?

Identifying children with the potential for myocardial recovery and supporting the heart to allow for (or even promote) recovery are important topics. Thus far, the durability and safety profile of early generation VADs and the lack of VAD experience at pediatric centers have limited the recommendation for LVAD placement with the intent of supporting a patient through a trial of myocardial recovery (10-11). If an LVAD were to be placed in a patient that was stable on inotropic support and recovery did not occur, LVAD placement could result in significant morbidity or lead to HLA sensitization and potentially worse pre-transplant outcomes. However, devices have improved and results continue to improve as experience is gained. That being said, germane to the topic of VAD placement for myocardial recovery is whether or not destination therapy is an acceptable option for children and young adults who are supported by a VAD but are not a candidate for heart transplant or do not want transplant. This is an important question to answer for children before one advocates for device therapy in an attempt to promote recovery.

How do we define "success" in myocardial recovery with respect to cardiac function and duration of improvement? To date, recovery has been defined in many different ways, including echocardiographic normalization, myocardial recovery, and heart failure remission. To measure cardiac recovery, we need to agree upon a definition of success including end points and duration.

This brings us to a third patient, "Mike". Mike required LVAD placement for acute anthracycline toxicity and inability to wean inotropic support. Seven months post continuous flow LVAD placement, he has shown evidence of myocardial recovery. An exercise test on full LVAD support reported a VO2 indexed of 25 ml/kg/min. An echocardiogram (LVAD turned down to lowest setting) showed low normal qualitative biventricular function with a 6 minute walk of 546 meters. After 4 weeks of decreased LVAD support (LVAD flow average of 1.5L/min) the qualitative echocardiographic function of both his right and left ventricles were mildly depressed, the BNP level increased from 158 to 723. His peak VO2 indexed went from 25 ml/kg/min on full support to 20 ml/kg/min. Clearly these findings raise concern for long term sustained myocardial recovery and many questions arise. What biomarker can best predict success or failure of LVAD explantation? Will unloading the ventricle for a longer period of time promote recovery or has the ability of mechanical support to promote recovery already run its course? Are the currently available adult LVAD weaning protocols predictive of sustained recovery and can they be applied to pediatric patients?

Steps toward understanding cardiac recovery:

1. Routine, serial assessment for myocardial recovery as part of heart failure management for patients supported by VAD (12).
2. Innovation of therapies that may uniquely benefit pediatric heart failure rather than extrapolation of adult trials and therapies (13).
3. Opportunities for discussion and debate on myocardial recovery including thorough review of the success stories, the recurrences, and the treatment failures.
4. Participation in multi-center studies and registries to find predictors for recovery and indicators of recurrence.

5. Use of tissue and blood banking studies to better understand recovery on the biochemical, cellular, and molecular level in pediatric heart failure.

To close with another quote by Charles Dickens from A Tale of Two Cities:

> *"A wonderful fact to reflect upon, that every human creature is constituted to be a profound secret and mystery to every other."*

Myocardial recovery may seem a "profound secret and mystery" at present, particularly in children with idiopathic, familial, or other "non-acute" causes of heart failure. Nevertheless, it is worth our effort to study myocardial recovery, look for recovery in children with heart failure, and to identify therapies that promote recovery. One of the best rewards in clinical practice is caring for the child with decompensated heart failure who experiences recovery.

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Pediatric Heart Failure: It's Finally Growing Up

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There is a well-known saying in pediatrics … children are not small adults. Yet, in pediatric heart failure, the majority of our therapeutic strategies, both medical and mechanical, are based on adult data, and progress within our field is somewhat stagnant when compared to adult therapies. This is due to the limited and sometimes conflicting published data on small numbers of pediatric heart failure patients. But in children the diversity in the underlying causes of heart failure, both from congenital and acquired heart disease make it difficult to extrapolate from adult trials. Overall, there has been lack of multi-center collaboration and data collection. In the November 2012 issue of Links, Dr Yuk Law wrote about these same challenges. He described how the growth within our field led to the development of the Pediatric Heart Failure Workforce, a subcommittee within the Pediatric Transplantation Council of the ISHLT. Over the past few years, the pediatric heart failure and transplant community has continued to grow and become more focused on developing research and therapies dedicated to heart failure in infants and children of all ages.

When faced with a child failing medical therapy and in need of mechanical support, I think most of us are quite jealous of our adult colleagues and their mechanical support options. The majority of centers treating advanced heart failure and performing heart transplants have become more and more comfortable using ECMO for short term support, but are placing ventricular assist devices earlier and more often with about 25% of transplanted pediatric patients being bridged with mechanical support in recent years (per the ISHLT annual report). The Berlin EXCOR, FDA approved for support in children, is the only option for babies and smaller children, but the size limits for the Heartware LVAD and Heartmate II LVAD are being pushed to give bigger children better long term therapy options.

In the July 2014 issue of Links, Dr. Janet Scheel and Dr. Angela Lorts highlighted the advances in pediatric mechanical support. Dr. Scheel discussed the PumpKIN trial, and NHLBI funded trial to assess the Jarvik 2000, a tiny continuous flow left ventricular assist device for infants and small children. Dr. Lorts gave an update on the progress with PEDIMACS, a registry that opened in 2012, dedicated to collecting data in the growing population of children supported on ventricular assist devices. The July 2014 issue also included the announcement of the monograph Volume 8: Guidelines for the Management of Pediatric Heart Failure. Currently, the ISHLT Pediatric Heart Failure Workforce is focusing their efforts on establishing a heart failure registry to capture prospectively the natural history of heart failure from cardiomyopathy and congenital heart disease. Until that data becomes available, the Workforce will also organize collaborative, multicenter cohort studies. A group looking into submitting a proposal to the NIH for funded studies has also spun off of the workforce. In preparation for the design of scientific studies, a survey to learn more about the current pediatric heart failure work force and training was conducted with the results to be published soon.

Interest in pediatric heart failure is also flourishing outside of the ISHLT. In September the 3rd annual Pediatric Heart Failure Summit took place in Cincinnati, OH. This conference is a two day event with presentations from leaders in the field highlighting recent data and advances surrounding pediatric heart failure and mechanical support.

In the past year, the American Heart Association (AHA) council on cardiovascular disease in the young (CVDY), with growing interest in pediatric heart failure, created a Pediatric Heart Failure Committee. The goal of this committee is to support the mission of the CVDY council to "improve the health of children with heart failure or cardiomyopathy through research, education, prevention, advocacy and quality improvement." The committee is supported by members of the CVDY council and from other councils within the American Heart Association, including a liaison with the ISHLT. The committee will focus on education and programming dedicated to pediatric heart failure for AHA scientific sessions and other conferences. The group will also explore opportunities to develop scientific statements and open the doors for collaboration with other pediatric heart failure groups.

The future is bright for the growing number of providers dedicated to taking care of children with heart failure, whatever the etiology may be. With continued momentum and collaboration within the different interest groups, we will be able to practice more evidence based medicine, learn from each other, and in the end, take better care of these fragile children. Yes … the field is growing up.

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Differential Response to Medications between Children and Adults with Heart Failure

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Although the pathophysiology and treatment of adult heart failure (HF) is well studied, HF in children remains poorly understood with most clinical treatment paradigms based solely on experience in adults. Emerging experimental evidence and epidemiologic data confirm that the pediatric HF population distinctly differs from adult HF patients. The heterogeneous nature of pediatric HF and the lack of associated co-morbidities in children (eg diabetes, hypertension) prevent direct extrapolation of adult-based therapies [1,2]. The most common cause of end-stage HF and indication for heart transplantation in infants is congenital heart disease, while dilated cardiomyopathy is the most common indication for transplant in children over the age of 1 year [3]. The combination of age, heart failure etiology and differences in medication pharmacokinetics and metabolism in children complicates the ability to identify the most efficacious therapies [4]. In addition, while adult HF survival has improved with the advancement of medical and surgical HF therapies, the outcome for children with HF has remained largely unchanged, which also suggests dissimilar pathophysiology [2,5].

Prospective medication trials in pediatric HF are scarce due to the rarity and diversity of the disease process as well as funding challenges. While the vast majority of adult HF clinical trials that inform clinical practice are industry-sponsored, the cost-effectiveness of supporting pediatric-specific HF drug development cannot be demonstrated due to the small population size. In the few pediatric clinical HF studies that have been performed, the results speak against the assumption that children will respond in the same way to HF medications as adults. The industry-supported pediatric carvedilol study is the largest randomized, controlled prospective HF drug study in children to date [6]. This study took over 5 years to enroll 161 children with symptomatic HF and there were no differences in the outcome measures studied. The results of this study have been widely challenged primarily due to study design, which included children with complex single ventricle forms of congenital heart disease as well as cardiomyopathies, and the higher than expected spontaneous improvement of enrolled patients. There have been a few small placebo-controlled, prospective studies of ACE-inhibitors and angiotensin receptor blockade in those with a single ventricle or a systemic right ventricle and results again have been negative or equivocal [7-10]. In many of these studies, the patients enrolled were considered to be at risk for HF given underlying anatomy, but did not have the clinical syndrome of HF, making these findings difficult to interpret.

There is an evolving body of evidence demonstrating important underlying age- and disease-related differences in myocardial HF pathophysiology. For example, there is a differential pattern of β-receptor down-regulation and microRNA expression in explanted end-stage failing left ventricles from children compared to adults with non-ischemic dilated cardiomyopathy [11,12]. Failure of the right ventricle is an important and increasingly common clinical problem, as children with severe forms of congenital heart disease are surviving into adulthood. There are no proven therapies for right ventricular failure and data from human and animal studies suggest that the right ventricle has a distinct response to pressure and volume overload with a unique pattern of gene expression, β-receptor regulation and signaling and microRNA expression compared to the failing left ventricle [13,14].

When considering all of the above, perhaps the most important conclusions from the current body of literature on pediatric HF therapy should be: (1) we cannot assume that children with HF will respond in the same way as adults to medical therapies, (2) ventricular morphology is an important consideration for HF therapy, (3) performing appropriately powered prospective clinical trials in pediatric HF may not be practical and (4) novel approaches to the identification of efficacious therapies for children with HF are needed. In the field of adult HF a significant body of evidence is needed before a change in clinical practice is accepted. This body of evidence often starts at the bench with human tissue, molecular and animal model investigations followed by drug development, pre-clinical and then multiple clinical trials demonstrating efficacy in large populations of patients. Because it is not practical to employ this adult paradigm to children, innovative approaches that minimize risk to children and combine findings from molecular studies (utilizing biorepositories, cell and animal models), genetic and biomarker investigations, longitudinal data obtained from large registries, computer modeling and worldwide collaborations are necessary. Increased awareness of the differences in children and adults with HF must lead to a renewed push for investment by government and foundation funding agencies in pediatric HF research and drug development if outcomes are to improve.

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The Science and Fiction of ABO Incompatible Transplantation

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History:
The ABO blood group system, which was first described by Nobel Laureate Karl Landsteiner in 1901, is based on polysaccharide antigens expressed on red blood cells. These antigens are also expressed on a variety of other cells including vascular endothelium. Consequently following some disastrous early experiences it was recognized that transplantation of solid organs across ABO blood group incompatibility mostly led to hyperacute rejection and loss of the organ, and, in the case of heart transplantation, associated loss of the patient. Adults and older children are regularly found to have preformed antibodies against their non-self blood group, predominantly but not exclusively of IgM type. The lack of expressed A or B antigens makes blood group O persons universal donors while the presence of both antigens in AB humans and consequent absence of antibodies to either blood group make them universal recipients.

Observational and experimental studies in the 1960s revealed that newborns completely lack agglutinating antibodies against the blood groups and typically only develop them between 6 and 18 months of age, sometimes even later. Contact to human blood or tissue is not required, but molecular mimicry and cross reactivity with the surfaces of intestinal bacteria induce the immune response that also agglutinates and non-self erythrocytes causes their lysis.

Driven by a desperate wait list mortality with only half of the newborns and infants surviving to transplantation, a team at the Hospital for Sick Children in Toronto under the lead of Dr. Lori West and Dr. Ivan Rebeyka planned to cross this assumed insurmountable barrier in carefully selected children who had not yet developed relevant quantities of blood group antibodies. In 2001 the successful intentional ABO incompatible (ABOi) transplantation of the first 10 infants of whom 8 survived at least for 11 months post-transplant was reported [1], breaking with a dogma and initiating a new view on transplantation in young children.

Immunology:
In the initial cohort, none of the patients had shown antibody mediated rejection including 2 of 8 surviving children who eventually developed antibodies towards the blood group antigens of their donor. Further follow up revealed an unprecedented finding of antigen specific tolerance in these patients: the vast majority did not develop antibodies or detectable B-cellular immune response towards their donor blood group [2]. Recent assessment shows that to present none of the patients has developed titers higher than 1:32 towards their donor [3] compared to average titers of 1:256 in healthy children older than 2 years. It is well illustrated that this difference is not the consequence of global immune suppression in blood group O individuals who have received incompatible hearts: recipients of blood group A hearts develop normal titers towards blood group

B but absent or very low titers to blood group A. The reverse pattern was documented for O recipients of B hearts and persistence of this tolerance was found up to 15 years post-transplant [4]. In addition, the isoagglutinins towards the donor blood group measured in erythrocyte agglutination tests of stepwise diluted plasma, which in principle are performed with the same laboratory technique as 100 years ago, is questionable. Recent investigations suggest that the endothelium of the heart expresses only some of the antigen subtypes and that antibodies towards these subtypes remain absent.

So which are the unique features of the immature immune system that allow indeterminate tolerance of the non-self blood group antigen, and until which age do they persist? The absence of the AB-blood group system and low potency of antibody mediated rejection in small rodents makes the generation of animal models difficult. Crucial hints on the mechanisms were drawn from infectious disease and vaccine research. Many pathogenic bacteria are protected by polysaccharide capsules of similar structure to the blood group antigens. Infections with these bacteria are more frequent and more severe in the same age range that permits AB-tolerance. Pure polysaccharide vaccines towards these infections were found not to induce antibody response up to 2 years of age. Polysaccharides cannot be presented in the type II major histocompatibility complex and therefore not induce the classical T cell mediated B cell response. Alternate activation of B cells occurs though linkage of the B cell co-receptor component CD21 to complement factor C3d bound to the antigen. While CD21 was found to be lacking in the spleen of children in the first 6 months of life, our group recently showed significantly reduced C3d levels specifically in children after ABOi transplantation [5]. Lipopolysaccharides can also be presented to NKT-cells via CD1d, a surface structure shown on regulatory B cells in mice and humans. While we found infants to have between 10 and 100 times the proportion of this B cell phenotype (CD5+CD1dhi) a correlation to ABOi transplant was not identified. In contrast, the development of B cell memory was shifted to less non-switched IgM+ memory B cells after ABOi compared to compatible transplantation. Further studies have to assess whether these immune alterations lead to consequences in immune response towards other antigens. To our surprise we found that infants after ABOi transplantation were significantly less likely to develop class II HLA antibodies compared to ABO compatible recipients [6], so ABOi transplantation might provide a tolerizing effect towards other donor antigens as well, although the power of this finding is low due to small numbers of patients and warrants verification in future studies.

From desperate experiment to standard procedure:

The 2001 paper induced huge attention and fascination; however, as every breach of long term dogmas, it also induced skepticism and limited adaption into clinical practice. Canada continued to pioneer the approach after 2001 from East to West. The two major centers in the United Kingdom and one German center could reproduce the Toronto success and publication of their safety data along with the encouraging long term results from Canada eventually convinced the US policy makers to offer this approach. The initial approach in the US was very careful: ABOi allocation only to patients with titers below 1:4 in the first year of life and only if the organ could not be compatibly allocated. Based on several studies showing that rejection rates and clinical outcome were similar despite selection of a sicker and higher risk cohort for ABOi hearts [7], UNOS revised their policy in 2013 to a more liberal ABOi allocation process, closer to the standard practice in the

UK and Canada. Other jurisdictions remain hesitant despite the increasing evidence of the safety of ABOi transplant in infants and the associated shortening of wait times and, in some studies, reduction of wait list mortality.

While from a Canadian point of view it appears almost unethical not to offer ABOi transplantation to infants, the applicability for older children and adults remains hazy. The UK cohort published in 2008 included a 4.5 year old patient with primary and a 7 year old child with ABOi re-transplantation. Meanwhile, our center has successfully performed several cases in children up to 4 years old, and oral presentations at the last ISHLT meeting mentioned toddlers ABOi transplanted in the UK. A Swedish group has published the successful ABOi transplantation of two carefully selected adult patients in 2012.

Looking beyond the heart:
Doctors in Japan have developed extensive experience with ABOi kidney transplantation due to the lack of a deceased donor program until recently. Using intensified immune suppressive regimes, outcomes were found to be vastly comparable to ABO compatible transplants. Early approaches including splenectomy were replaced by routine application of B-cell depleting agents (rituximab); however, recent data suggests that even this may not be required. From an immunological perspective there are no overt reasons why infants receiving ABOi liver or lung transplants should not follow the same course as observed in the heart patients since the key to success seems to lie in the maturity of the immune system rather than in the type of transplanted organ.

Where do we go from here?
ABOi transplantation provides a unique insight into mechanisms of the human immune system and its immaturities. It may reveal some of the reasons why children show the best long term graft-survival of all age groups after heart transplantation. Whether targeted intervention such as interruption of B-cell maturation can induce similar benefits and ABO-tolerance in the more mature immune system remains undetermined but should be the subject of future research.

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Recognizing an Unmet Need: The Role of a Patient and Family Advisory Council in Heart Transplant Care

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With the arrival of new hospital leadership at Stanford Health Care in 2011, the movement to patient and family centered care received a new sense of urgency. This change matched well with discussions that were well underway within the heart transplant program. The Heart Transplant Quality Council, a multi-disciplinary group representing all areas of the heart transplant program and hospital units of care, felt that the active involvement of patients and family members in their care could significantly aid in achieving target quality metrics, such as length of hospital stay and readmission rates, which were just then being formulated. A key element would be a Patient and Family Advisory Council.

The heart transplant program Patient and Family Advisory Council (PAFC) met for the first time in the fall of 2011. The initial configuration included one faculty and two staff members, four transplant patients and one family member. The meeting was the result of a year-long process engaged in by heart transplant program staff to draft initial bylaws, identify and interview over 30 possible candidates, and coordinate heart transplant program plans with the broader initiative of providing patient and family centered care.

The council moved quickly to begin work. Its first activity was to seek out the other major heart transplant centers in the US and ask them if they had a PFAC. If the answer was yes, the council asked a range of questions to develop an understanding of how it was founded, how it operated, and lessons learned. The council soon learned that only a handful of centers had a PFAC and that few were formalized. Of those that did exist, they were young and only beginning to articulate best practices.

Armed with this finding, the council generated a list of high impact projects and began with an ambitious vision of developing a patient and family centered website. The site had the dual purpose of building community and answering non-clinical questions for patients and family members at all stages of their transplant journey. The newly developed content was published in mid-2012 as part of the Stanford Health Care website. A subsequent review of the web data showed the site to have received over 11,000 views in 8 months with viewers staying on each page several minutes. The time spent on each page indicates that viewers are actually reading the content made available to them.

The PFAC also wanted to take concrete steps to revive the sense of community among transplant recipients, family members, and hospital staff. This effort culminated in the 2012 heart transplant community reunion, which drew over 300 attendees. The response was so positive that the PFAC decided to reprise the event in 2013 with the understanding that it would be an annual event. In response to 2012 attendees' feedback, the 2013 event also included a mini symposium where current topics in heart transplant research were presented in lay language. The showcasing of some of Stanford's leading edge research inspired patients and family members and helped them see beyond their experience to the future of the larger transplant community. We also added a video of thanks from patients celebrating the living of their everyday lives. And, as was done the year prior, we invited a patient speaker to tell her story and concluded the program with a formal recognition of all recipients from prior years, starting from the immediate past year and going back over 25 years. Recognizing our 25+ year recipients ended the evening on an inspirational note for patients, family members, and staff.

At the time of the PFAC's formation, members had been serving informally as Peer-2-Peer (P2P) contacts for people in various stages of the transplant process. With the beginning of a formal hospital sponsored P2P mentoring program, the heart transplant PFAC volunteered to be the first class for the newly developed P2P training program. In 2013 two more transplant patients joined the council, and all eight patient and family members are now active P2P mentors.

In 2013 the Heart Transplant Quality Council established a seat for a patient to become a member of the council. The position is currently filled with one of the PAFC's founding members, and the attendees of this bi-monthly meeting have accepted the patient participant as a valued member of the team. When issues come up where a patient perspective would be of value, members of the council have come to desire the patients' perspective and come to rely on it to better the program.

As the PFAC begins its fourth year, there is a sense of accomplishment and enthusiasm for what lies ahead. The PFAC is currently writing our two year plan and recruiting members. Our 2015 projects include a focus on raising donor awareness and enhancing understanding and access to complementary and alternative medicine (CAM).

In addition, a new hospital designed explicitly to address the concerns of patients and their families, will open in 2018. The PFAC has had a voice in the planning and will continue to be involved. This is an example of the PFAC adding value beyond the transplant program to the entire health care enterprise at Stanford. It is rewarding to have a seat at the table and to have our voices be heard after three short years of growth. In partnership with the health care team at Stanford, we feel confident our contribution is bettering the program for all.

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US Heart Allocation Policy: Current Issues and Possibilities for Fix

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US heart allocation policy has evolved considerably since the inception of the National Organ Transplant Act in 1984. An urgency-based system with concentric geographic zones was first adopted in 1988, with 2 priority statuses: Status 1, for all mechanical circulatory support (MCS) patients and those with inotropic dependency, and Status 2 for everyone else. Further modifications occurred in 1998 saw the introduction of a 3-tiered system, with Status 1A, the most urgent, intended for patients supported with MCS, mechanical ventilation, inotropic dependency with continuous hemodynamic monitoring, Status 1B for stable patients on ventricular assist devices (VADs) or inotrope infusions, and Status 2 for all others.

The current system, which was last modified in 2006, allows greater regional sharing of organs according to clinical urgency; thus, organs are now offered only to Status 1A/1B candidates locally (organ procurement area), then in the nearest concentric zone (500 mile radius) before being offered to Status 2 locally. Each policy change has sought to meet the government defined "Final Rule", which prescribes the difficult combination of equitable organ allocation (including across regions) while prioritizing according to objective severity of illness. Despite this, status 1A mortality in particular remains high [1].

Even with the most recent 2006 policy change, there remains regional heterogeneity in waiting times and number of transplants performed on higher urgency candidates. In particular, Region 1 of the US has demonstrated increased waiting times for status 1A patients [2], in part due to poor access to donors. In order to provide more equitable access, the Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) Thoracic Committee is considering methods to enable broader regional sharing of hearts, either through the designation of geographical zones according to projected donor population, or greater priority for neighboring zone Status 1A patients over local Status 1B patients.

Since 2006, the widespread use of continuous-flow ventricular assist devices has prolonged survival and decreased mortality in waitlist patients [3], leading us to reconsider the urgency of transplanting stable VAD patients. The prolonged survival is reflected in the fact that waitlist numbers of Status 1A/1B patients have tripled since 2006 [1]. On the other hand, patients with VAD complications have been established to fare worse [4] and should remain highly prioritized.

Current policy development also seeks to assign higher priority to particular subgroups within Status 1A/1B that are at a disadvantage under the current system, with increased waitlist time and risk of mortality. These include those patients with restrictive cardiomyopathy [5], amyloidosis [6], congenital heart disease [7] and highly sensitized patients [8]. For highly sensitized patients, a

uniformly standardized definition must be met, both in terms of unit of measurement (e.g. cPRA) and the method by which this measurement is obtained. For example, the Canadian definition of a highly sensitized patient is that of a patient possessing a panel reactive antibody (PRA) >80%, or PRA >20% with 3 prior positive crossmatches (in the setting of negative virtual or actual donor/recipient-specific crossmatch and appropriate size and blood-type of the prospective donor) [9].

How then, to be as fair as possible to all these subgroups? A heart allocation score, analogous to one used by our colleagues in lung transplantation, has been raised as a possibility. However, there are concerns about the length of time it would take to develop such a score, especially in a field that is so rapidly changing. In addition, there are fears that the data currently collected by the OPTN from transplant programs is incomplete and may lead to inappropriate scoring.

A multi-tiered system appears the most viable solution at present; one is currently in development by the OPTN/UNOS Heart Subcommittee, following the example set by our colleagues in the Eurotransplant countries, France, United Kingdom, and Canada. Such a system is overwhelmingly favored by centers across the United States [10], and would specify a clear prioritization level for each subgroup, reducing the need for status exceptions.

In summary, recent changes in the field of heart failure and transplantation have resulted in greater waitlist numbers, while status 1A mortality, although decreased, remains high. As it has done with each iteration, US heart allocation policy must inevitably continue to adapt to comply with the "Final Rule". Future policy must also address ethical issues such as multiple listing and retransplantation. For now, a further-tiered system with modified geographic zones appears to be the answer.

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Enterovirus D68 is Making the Rounds

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The late summer cold season has been dominated by dramatic coverage of Enterovirus species D 68 (EV-D68) by most major media outlets. Many showed footage of busy Emergency Rooms and small children receiving breathing treatments. Initially reported as the 'Mystery Respiratory Virus' by some, it was subsequently determined that a strain of enterovirus was largely responsible.

Enteroviral infections are common, often asymptomatic, and typically occur in the summer and fall. When symptoms do occur, they vary widely and in immune competent hosts may include mild upper respiratory infection, fever with rash, and neurologic illness, such as aseptic meningitis and encephalitis. Enterovirus infections in transplant patients are not frequently reported, but have been most often documented in stem cell transplant recipients [1,2]. In contrast to the other enteroviruses, EV-D68 primarily causes mild to severe respiratory illness.

EV-D68 was first isolated in California in 1962 [3], and was infrequently reported as a cause of illness until the last few years. Between 2008 and 2010, there were outbreaks of respiratory illness associated with EV-D68 worldwide, including the Philippines (2008), Japan (2010), the Netherlands (2010), and the United States (2009-2010) [4].

This year has seen a well-documented increase in patients hospitalized with severe respiratory illness due to EV-D68 in Missouri, Illinois and a number of other states [5]. From mid-August through September 22, a total of 175 patients from 27 states were confirmed by either the CDC or the state public health lab to have EV-D68 [6], with more likely to be added.

EV-D68 infection is frequently seen in children, with peak incidence in those 0-4 years of age[4]. Underlying respiratory disease, such as asthma, appears to be the most significant risk factor for severe illness, and was seen in 68-73% of recently reported cases [5]. Frequently reported symptoms include cough, wheezing, dyspnea, hypoxemia, retractions, and perihilar infiltrate on chest radiograph [4,5]. Fever is less common, seen only in 18-26%. While there is likely some component of selection bias, it is notable that 19/19 patients from Kansas City, and 10/11 patients from Chicago required admission to the intensive care unit.

There are little data available regarding EV-D68 and solid organ transplantation. An analysis from the Netherlands of 24 patients with EV-D68 in 2010 included 3 lung transplant patients; all of whom survived [7]. With respect to donor organs, it is likely not advisable to accept lungs from a donor with suspicion for EV-D68 infection. While EV-D68 dissemination to the heart is unclear, enteroviruses have been found to be cardiotropic and associated with adverse clinical events in pediatric heart transplant recipients [8], potentially placing donor hearts from EV-D68 infected patients at higher risk as well.

Diagnosis of enteroviral infection is most commonly done with PCR testing. It is often not part of the standard 'respiratory panel' offered by commercial or institutional labs, and therefore may need to be requested separately. Further complicating diagnosis is the risk that some platforms may incorrectly identify EV-D68 as a rhinovirus. If EV-D68 is suspected, communication with the testing lab is advisable. Currently, specific testing for EV-D68 is available from the CDC and some state public health labs. CDC's Picornavirus Laboratory (e-mail: wnix@cdc.gov) is available to assist with testing.

There is no specific therapy available for enterovirus infections, care is supportive. Additionally, since this strain has not been circulating widely in recent years, it is unlikely, or at least unknown, if current supplies of intravenous immune globulin (IVIG) contain therapeutic quantities of EV-D68 type-specific antibody.

The above average number of ED visits and hospital admissions reported this season can place a significant strain on institutional resources. Experience in our community from early August thru mid-September demonstrated a 10-fold increase in ED visits for respiratory illness diagnoses compared to the same time period over the last two years, as well as a 10-fold increase in pediatric intensive care unit admissions for wheezing or respiratory compromise. The specific etiology of this increase is unknown, but the spectrum of disease appears consistent with that reported from Kansas City and Chicago. The direct impact of this increased volume has been to limit bed availability, which may influence a center's decision to proceed with transplant. It's unclear if this is limited to pediatric facilities, or will be seen in adult hospitals as well.

Currently, this enteroviral season appears to be heavily influenced by a strain with a preference for the respiratory tract, placing patients with underlying lung disease at much higher risk of severe respiratory illness. The CDC requests that health care providers should consider EV-D68 as a possible cause of acute, unex¬plained severe respiratory illness; and suspected outbreaks should be reported to local or state health departments [5].

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Andrew J. Fisher, FRCP, PhD
Daniel R. Goldstein, MD
ISHLT Grants & Awards Committee Co-Chairs
http://www.ishlt.org/boardsAndCommittees/grantsAndAwards.asp

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Host Institution: Stanford University School of Medicine, Stanford, California, USA

Zachary Kon, MD
Applicant's Institution: University of Maryland Medical Center, Baltimore, MD, USA
Host Institution: University of Toronto, Toronto, CANADA

Evgenios Neofytou, MD
Applicant's Institution: Stanford University, Stanford, California, USA
Host Institution: University Heart Center Hamburg, Hamburg, GERMANY

Dong Wang, MD
Applicant's Institution: University Heart Center Hamburg, Hamburg, Germany
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Editor's Corner: Smartphones, Traffic Lights, and the Mechanical Ventilator: A Circuitous Path

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Moore's law is an observation that technological power doubles with every year. The boom in technological advances has also affected our daily lives. The hallmark of the creative '60s was "tuned in, turned on and dropped out." Today we are simply "plugged in" from the start of our day to the finish, even "wirelessly." Try explaining that to ourselves in the 1960s. Today, we wake up to check our e-mail. We commute to work while listening to our pre-set radio stations. Even stopped at a traffic light, we reach for our smart phones to check for updates. Some of us are literally embedded with technology, ranging from pacemakers to being intubated on a mechanical ventilator in the ICU. There is no denying how linked we are to technology and each other.

What do traffic lights, cell phones, mechanical ventilators and pacemakers all have in common? Other than being electronic devices, these devices rely on a specific type of circuit to work known as the resistor/capacitor circuit, or RC[1]. Simply stated, an RC circuit is an electrical circuit comprising a resistor, or something that can resist electric flow, and a capacitor, an electrical element capable of building up a charge across two plates separated by a short distance[1]. These two elements are in series with one another so that electrical current produced by a power source provides an electrical potential difference, or voltage that passes through a resistor before charging the capacitor. The electrons flowing through this circuit generates a charge across the capacitor, storing energy. Capacitors can be seen in some of the smallest places, like the millions upon billions of 1's and 0's generated in a computer chip to the largest of places like the space between the earth and the atmosphere to produce a bolt of lightning. Generating charge in a capacitor takes time. The longer amount of time allowed to charge a capacitor, the more the potential charge across the capacitor plates increases. The charge across the capacitor can be expressed as:

$$V_c = Q/C$$

Where V_c is the potential difference across the capacitor. If one were to try to analyze V_c as a function of time, Kirchoff's loop rule would be required. There are two rules that Kirchoff created, one of which is the conservation of energy, so called the "loop rule". It states that the sum of all the changes in potential energy around a closed loop circuit must equal zero[1]. With this in mind, the electron motive force (emf) of a battery used to charge the capacitor in an RC circuit must equal the sum of all the voltage changes that occur throughout the circuit as the current flows through the resistor and the rest of the system as it tries to build up charge[1]:

$$Emf = IR + Q/C$$

Emf, R and C are kept constant while Q and I are functions of time[1]. In other words, the amount of charge that is built up into a capacitor is dependent on the rate at which charge flows through the RC circuit, or in calculus terms: I = dQ/dt. Substituting this into our previous equation, we get:

$$Emf = R(dQ/dt) + Q/C$$

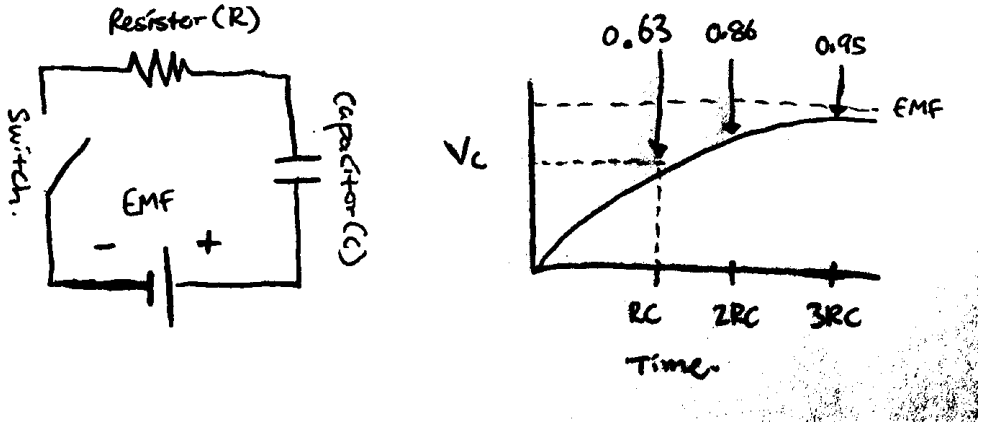
By using integration (I will spare you the derivation) and assessing the time it takes from the beginning of capacitor charging (time 0) to the time it takes to fully charge the capacitor, we are left with an equation that looks like this:

$$V_c = Emf\ (1- e^{-t/RC})$$

The RC term that is seen in this equation is known as the time constant[2], or:

$$\tau = RC$$

It represents the amount of time required for the capacitor to reach $1-e^{-1}$, or 0.63, or 63% of its full charge and voltage. The graph below shows that 2 time constants charges the capacitor 86% towards full capacity and 3 time constants charge up to 95%[1].

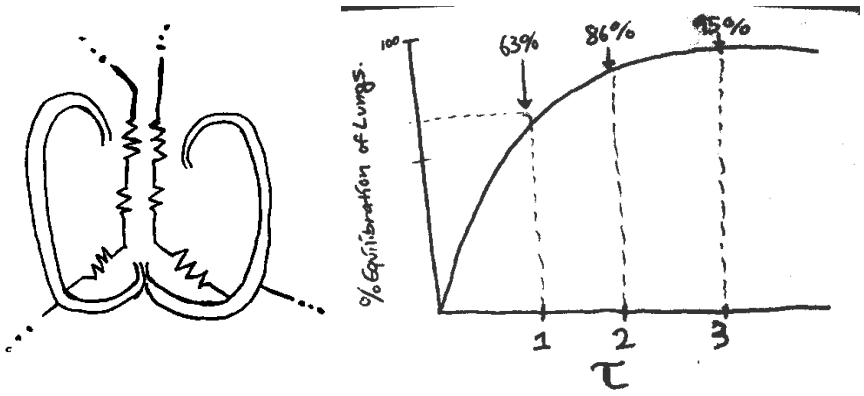


(Giancoli, *Physics,* 4th Edition)

Now what do traffic lights, smart phones, pacemakers, and the lungs have in common? Though it is not intuitive to think of the lung as an RC circuit, the two have many similar properties in terms of function and mechanics. If one were to imagine a lung as an RC circuit, the capacitance would be analogous to the compliance of the lung and the resistance of the circuit equivalent to the resistance of the airways. Just like an RC circuit, the lung also functions as a time constant that will depend on both resistance and compliance[3].

Resistance = Pressure change / flow rate
Compliance = volume change/ pressure change

This time constant is especially important in the ICU when pertaining to ventilator-dependent patients. The longer the time that is allowed for a lung to "charge up" like a capacitor, the more percentage of air will equilibrate within the lungs. In order for there to be adequate delivery and distribution of air (ventilation), a minimum of 3 time constants is needed. This corresponds to "charging up" the lung with gas to about 95% its capacity[4]. Therefore, in diseases where there are increases in resistance, compliance, or both the time constant increases thereby requiring a longer time to reach maximal "charge" of the lung, and vice versa (inflation/deflation). However in patients with ARDS, pulmonary edema or primary graft failure, they have highly elastic or stiff lungs with low compliances resulting in shorter time constants which mean that their lungs inflate and deflate at a faster rate than normal lungs leading to incomplete ventilation; rapid, shallow and ineffective ventilation. Also imagine a patient with obstructive pulmonary disease, where the conducting airways are constricted, leading to an increased resistance to flow. As a result, the time constant increases, therefore requiring a longer time constant in order to reach optimal lung ventilation[5].



(If one were to imagine the respiratory system as an RC circuit.)

One can apply this information in the ICU when managing a patient on a ventilator. How long should a patient's respiratory cycle be in relation to their current disease? Are their resistances increased or decreased? How about their compliance? All these aspects should be kept in mind when trying to properly ventilate and manage a patient requiring mechanical ventilation.

Who would have thought that an electrical physics concept would come to relate so perfectly to the respiratory system? Then again, medicine's relation to the physical and mathematical world has been present since the very beginning. As Neil deGrasse Tyson, a renowned astrophysicist, states, "We are all connected; to each other, biologically. To the earth, chemically. To the rest of the universe atomically." So in a sense, we have linked two seemingly unrelated concepts together.

Take a deep breath. Do you feel charged?

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