VINCENT’S TURKEY SENSE:

Starting In the Spotlight are the halftime reports from our President, Maryl Johnson, and our Program Chair, Jeff Teuteberg, who provide us important and insightful summaries of our vibrant, active and refining ISHLT for the better as we approach the 37th Annual Meeting and Scientific Sessions in San Diego. Next we are pleased to announce the launch of the New ISHLT Online Learning Platform. To get going with Pediatrics, Shriprasad Deshpande from Emory compels us to keep the right heart from being left out as we tend to the congenital heart disease population and Stephanie Handler shunts us around from the past to the present by providing us an historical account of the Pott’s shunt from 70 years ago and how it is applied today. For Pulmonary Hypertension, it’s Sophia Airhart and Amresh Raina of Allegheny Hospital in Pittsburgh describe the results of a multicenter trial of patients with pulmonary hypertension unburdened from the stigma of carrying a continuous infusion pump with the novel strategy of a totally implantable prostacyclin system. Then, in keeping with Thanksgiving, Ryan Davey delivers us from a famine, a feast of medical strategies for patients with pulmonary arterial hypertension before Kathy Tang and Guatam Ramani remind us of the fable from Aesop on the benefit of slow and steady over haste and waste with nearly a quarter of century of prostacyclin for pulmonary arterial hypertension. As Special Interest pieces, Lori Bowser shares her perspective with us of her father’s journey with an LVAD, comparing him to Superman as he goes deer hunting as a hospice patient. Next, Maryanne Chrisant enlightens us from her recent interview with an atheist and his experiential perspective as a palliative care specialist from New York on pain and suffering before your Editor-in-Chief closes this issue on keeping the Arts in mind as we care for our patients with pain and suffering. Your dedication and devotion to your patients will always make a difference.

Happy Thanksgiving!
IN THE SPOTLIGHT: Your President’s Halftime Report

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It doesn’t seem possible that I have reached the midpoint of my ISHLT presidency! During my first 6 months, I have continued to be impressed by the dedication of our members and the commitment of our leaders and staff to move the ISHLT forward. In late September, Amanda Rowe and I had a series of conference calls with the Council Chairs and Board Liaisons during which we learned of the challenges faced by them and tried to provide suggestions as to how important initiatives might be moved forward. Last weekend we further opened lines of communication when the ISHLT Board and Council chairs met at Normandy Farms Inn outside Philadelphia for a retreat and Board meeting. This was felt to be a grand success by all and hopefully will serve as a firm foundation for ISHLT leaders to work together more closely in the future. Not only were we able to get to know each other better, but in several brainstorming sessions we discussed how the Councils, Council leaders, and Board can communicate and collaborate better to strengthen the ISHLT and allow the ISHLT to accomplish its mission.

The ISHLT Board, Governance Committee, and Staff have been working hard to move forward the objectives defined as first year priorities in the 2016-2020 ISHLT Strategic Framework. As reported in the May and August issues of the LINKS, the Board selected 6 objectives, representing items from all of the agreed upon Strategic Imperatives, as priorities for this year. I am happy to report that progress is continuing to be made on nearly all of them, as indicated below:

<table>
<thead>
<tr>
<th>Strategic Imperative</th>
<th>Objective</th>
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| Enhance Membership Value             | Offer access to ISHLT educational opportunities throughout the year  
  - A Webinar section has been added to the Education tab on the ISHLT website where members will be able to view content “on demand” free of charge. The focus will be to provide content that has already been recorded at the Annual Meeting, but there is also a webinar being produced by the NHSAH Council that should be available in the near future. The 2016 MCS Core Academy is presently available and additional prerecorded offerings will be added in the future. |
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<tr>
<th>Enhance Membership Value</th>
<th>Upgrade ISHLT website to improve accessibility/connectivity/device independence</th>
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<td></td>
<td>A web-site task force has been created, chaired by Michael Petty with members including David Baran, Alejandro Bertolotti, Mark Greer and Manreet Kanwar. This group has been tasked to work with ISHLT staff (and outside consultants as necessary) to plan the website upgrade with a goal of having the updated website available by the time of the 2018 Annual Meeting.</td>
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<td>Enhance Membership Value</td>
<td>Use Webinar format to facilitate quarterly Council meetings during the year and enhance interdisciplinary Council discussions</td>
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<td>A survey of the Council Chairs suggested that an online meeting platform outside the Annual Meeting was less of a priority than increasing member networking opportunities at the Annual Meeting, so the latter will be pursued first.</td>
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<td>The Board Conference call in December will use an online platform so content can be projected by Amanda for Board members to view during our discussions. Depending on how beneficial this is, a similar platform may be made available for future Council leadership or Council member calls.</td>
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<td>Engage Our Community Worldwide</td>
<td>Collaborate with 3 existing regional/national societies to increase outreach for education and research in heart &amp; lung disease</td>
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<td>On the July Board conference call, new policies for ISHLT participation in joint educational activities (In Kind Educational Grants and Endorsements) were passed by the Board. These policies and the application forms for applying for these types of activities, in addition to those for other approved educational activities, can be found in the Education tab on the ISHLT website.</td>
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<td>It was decided that priority topics for educational collaborations would be 1) Mechanical Circulatory</td>
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<td><strong>Improve Science &amp; Drive Innovation</strong></td>
<td><strong>Ensure Organizational Vitality</strong></td>
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<td>Support; 2) Heart and Lung Transplantation; and 3) Pulmonary Hypertension. Regions of the world prioritized for collaboration include 1) Latin America and the Brazilian Transplantation Society; 2) Asia Pacific and 3) Eastern Europe. I2C2 leadership is working with staff and local organizations to facilitate the submission of appropriate applications for Board approval to move forward with collaborative educational events in these areas.</td>
<td>Establish an ISHLT Research Quality &amp; Innovation Task Force to explore greater partnerships with outside sources of funding</td>
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<td>- Although deemed to be very important, this objective was postponed by the Board as it is really a tactic of a larger initiative that will consume considerable volunteer, financial, and staff resources. It will be reconsidered by the Board within the next year.</td>
<td>Create a formal Governance Committee with 3-year terms of office and representation from Past Presidents and Past Board members</td>
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<td>- A Governance Committee has been formed, chaired by Duane Davis and including Paul Corris, Andy Fisher, Richard Kirk, Stuart Sweet, David Taylor and me.</td>
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<td><strong>Ensure Organizational Vitality</strong></td>
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<td>Develop roles/responsibilities for all organizational units (Board/Committees/Councils) and volunteer positions</td>
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<td>- The Governance Committee is holding conference calls every two weeks to work toward developing job descriptions for all ISHLT organizational units and volunteer positions. The ambitious goal is to have these developed by the time of the 2017 Annual Meeting.</td>
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We had previously reported that we would reassess the remainder of the Strategic Framework and decide which objectives to move forward next. The Board carried out this task at our recent Board meeting and decided upon the following objectives as the next priority:

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<th><strong>Strategic Imperative</strong></th>
<th><strong>Objective</strong></th>
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<tr>
<td>Enhance Membership Value</td>
<td>Improved access to annual meeting content for those unable to attend</td>
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<td>Enhance Membership Value</td>
<td>Provide better opportunities for Council member networking at the Annual meeting</td>
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<td>Enhance Membership Value</td>
<td>Increase networking potential of the ISHLT Links</td>
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<tr>
<td>Engage our Community Worldwide</td>
<td>Be a resource to countries trying to establish their standards of care in this field by sharing practice guidelines</td>
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<tr>
<td>Improve Science &amp; Drive Innovation</td>
<td>Provide timely feedback to the hospitals on their performance (using Registry data)</td>
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<tr>
<td>Ensure Organizational Vitality</td>
<td>Establish a Leadership Development Committee with 3-5 year terms of office and representation from Past Presidents. Responsibilities to include:</td>
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<td>a. Develop process for identifying potential future ISHLT leaders</td>
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<td>b. Develop process for mentoring and assessing the identified potential future ISHLT leaders and placing them into positions of responsibility</td>
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<td></td>
<td>c. Develop plan for expanding current pool of individuals eligible to serve and with the necessary skill set for serving effectively as an Officer of ISHLT</td>
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As with the objectives prioritized for the first year, ISHLT leaders will be working with Staff to define specific tactics to move these additional objectives forward. ISHLT Councils and Committees are also encouraged to keep the Strategic Framework prioritized objectives in mind as they develop project proposals to bring forward to the Board.

Yes - - your ISHLT is alive and well and moving forward every day! Please read the Program Chair’s Report in this issue of the LINKS and visit the Annual Meeting website to learn more about the exciting 2017 Annual Meeting to be held in San Diego in April, 2017. You won’t want to miss the educational content and networking opportunities it will provide, so make your plans to attend NOW!

Disclosure statement: The author has no conflicts of interest to disclose.
IN THE SPOTLIGHT: Update from the 2017 Program Chair

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The end of October brings colder weather, changing leaves, Halloween and the ISHLT abstract deadline. The 2017 Program Committee had a busy summer and fall preparing for the meeting in San Diego, but the final program is now complete and available online as a PDF or flip book. Once again I would like to thank the membership for all of their fantastic submissions, the Program Committee for all their time and diligence, and the ISHLT staff for their support and guidance. This year’s Plenary Sessions will have more featured abstracts than in past years and the plenary presentations should have a little something for everyone, from stem cells, to social media, to novel means of funding drug development.

Now that the abstracts are submitted we are undertaking the review process with the Abstract Selection Committee. Each abstract will have over 10 reviewers and once the scores are assigned, the Committee will divide the accepted abstracts to oral, mini-oral or poster sessions. All of the oral abstracts will then be organized into sessions of six abstracts with a common theme and placed into the conference schedule. Last year there were a record 1516 abstracts and I am hoping we can match or exceed that this year. From the abstract deadline on October 25 the Committee only has until the first full week of October to grade, categorized and organize all of the abstracts. On the weekend of December 9th the Committee will meet in Dallas to finalize the selected abstracts and place them into the program. Megan has also promised that she would teach Andy, Chris and me to two-step, but with any luck there will be no photographic or video evidence that might “find” its way into a plenary session!

As the cold grip of winter descends upon the northern hemisphere, what better way to chase away the winter blues than to book your trip to sunny San Diego in the spring? For those of you in the southern hemisphere, well, keep that summertime vibe going and book your rooms as well! It is never too late to register for the meeting, reserve your hotel and confirm your travel plans. Keep an eye out in your email, the website and Links for more updates and highlights for the 37th Annual Meeting.

Disclosure statement: The author has no conflicts of interest to disclose.
NEWS & ANNOUNCEMENTS: New ISHLT Online Learning Platform Launched

In April 2016, the ISHLT Board approved a new Strategic Framework to guide the work of the Society over the next 5 years (add small version of attached graphic to LINKS). One of the Strategic Imperatives of this new framework is Enhance Membership Value. In this era of waning participation in membership organizations, ISHLT is fortunate to be experiencing membership growth. We want to continue to grow the Society’s membership, but we also want to retain our current members whose engagement and participation are highly valued. The aim of this strategic imperative is to make the current ISHLT programs and services more valuable to our members and to increase the number of programs and services available only to ISHLT members. As such, one of the Goals for delivering this Strategic Imperative is to Provide Access to Education Using Innovative Platforms. And one of the Objectives to achieve that goal is to Offer Access to ISHLT Educational Opportunities Throughout The Year.

Strategic Imperative: Enhance Membership Value
Goal 1: Provide access to education using innovative platforms
Objective 1: Offer access to ISHLT educational opportunities throughout the year
Tactic: Free on-demand webinars for ISHLT members

The means by which ISHLT will initially deliver on this Objective is via a new Webinar platform that was launched in October. This Webinar platform will be the portal for ISHLT members to access ISHLT educational content on demand and free of charge. The Webinars will initially consist of video recordings of the 2016 Academy: Core Competencies in Mechanical Circulatory Support (available now). In November 2017, we plan to add a 1-hour webinar on E-Health delivery, created by the Nursing, Health Sciences, and Allied Health Council. In April 2017, additional webinars will be added to include the 2017 Annual Meeting Plenary Sessions, and in September 2017, additional webinars will be added to include the following:

- 2017 Academy: Core Competencies in Heart Failure and transplantation
- 2017 Academy: Core Competencies in Mechanical Circulatory Support
- 2017 Academy: Core Competencies in Pediatric Mechanical Circulatory Support
- All Symposia from the 2017 Annual Meeting

Through these Webinars, we intend to provide access to free professional education throughout the year to those members who are unable to participate in person at the Annual Meeting and/or the Academies. CME and CEU will not be provided for Webinars.

To learn more about ISHLT Webinars and to access the 2016 Academy: Core Competencies in Mechanical Circulatory Support Webinar, click here: http://ishlt.org/education/webinars.asp
High PVR and Pediatric Heart Transplantation: Right Heart Should Not Be Left Out!

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Elevated of pulmonary vascular resistance is considered a relative contraindication for heart transplantation. As is true with other circumstances such as ABO incompatibility or very high PRAs, elevated PVR continues to be a moving target.

The elevation of PVR is thought to be a remodeling response to chronic elevation of LV end-diastolic pressure and low cardiac output. In patients with congenital heart disease, additional factors such as Fontan physiology, abnormal pulmonary vasculature and chronic exposure to left-to-right shunts contributions to high PVR.

Impact of elevated PVR especially on the right ventricle post heart transplantation is a critical area of concern that is under investigated. Additionally, increasing burden of adult congenital patients may substantiate this problem further.

The initial UNOS analysis by Davies et al (2008) [1] identified a PVR of > 6 WU along with elevated creatinine and high PRAs as risk factors for mortality. Over the last 5 years, there have been few additional reports outlining pediatric experience with elevated PVR and outcomes in pediatric heart transplantation. In 2010, Daftari et al [2] reported outcomes in 7 patients with elevated PVR (mean 11.0 WU) that were treated with sildenafil or bosentan preoperatively and managed with sildenafil, iloprost and inhaled nitric oxide postoperatively. They report 100% survival at one year. However, a report from 2011 by Ofori-Amanfo [3] concluded that patients with elevated PVR, especially those with poor response to acute vaso-dilatory therapy had significantly higher incidence of RV failure and mortality compared to those with normal PVR. Singh et al (2014)[4] report experience of treating post-transplant high PVR patients with sildenafil. 24 patients treated with sildenafil demonstrated an improvement in PVR, mean PA pressures and RV function with therapy. Overall, although there is sparse data, early and aggressive treatment of elevated PVR pre-and post heart transplantation seems to improve outcomes. Similarly, close monitoring of the right ventricular function as well as preemptive and early therapy of right ventricular failure is critical in avoiding morbidity and mortality related to RV failure post-transplantation. The current update to the ISHLT guideline (2016) [5] identifies the need for thorough evaluation of PVR in pediatric patients especially those with congenital heart disease. The guidelines emphasize that response to acute vasodilatory testing to differentiate between ‘reversible’ vs ‘irreversible’ PVR may be critical. Additionally, the role of ventricular assist devices in assessing chronic remodeling and reversibility of PVR needs significant research in pediatric patients. As a community, establishing guidelines for pediatric transplant candidacy in the setting of high PVR, better data regarding outcomes, thresholds for early initiation of therapy will help improve management and outcomes of these patients.
Disclosure statement: The author has no conflicts of interest to disclose.

References:


What’s Old is New Again: Palliative Potts Shunt in Children with PAH

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Despite advances in medical therapy and continued approval of new drugs to treat WHO Group 1 pulmonary arterial hypertension (PAH) in adults, 5-year survival for pediatric patients is still only 74% [1]. Even with initial symptomatic improvement in patients on prostacyclin therapy, many experience a decline in right ventricular systolic function associated with worsening functional class due to disease progression. In those patients, lung transplantation has been the only option.

The Potts shunt (direct anastomosis of left pulmonary artery to descending aorta) was first performed in 1946 at Children’s Memorial hospital in Chicago by Dr Willis J Potts as a “blue baby” operation to provide pulmonary blood flow for cyanotic congenital heart disease. Palliative ‘reverse’ Potts shunt in which flow is directed from the pulmonary artery to the aorta was first described in 2 children with PAH in the New England Journal of Medicine in 2004 by Dr Blanc and colleagues [2].

The concept of converting a failing right ventricle into ‘Eisenmenger physiology’ with a ‘pop-off’ to the systemic circulation to maintain cardiac output is appealing given the improved survival of adult patients with Eisenmenger physiology compared to those with idiopathic PAH [3,4]. The same survival benefit was not seen in the REVEAL registry analysis of pediatric patients with Eisenmenger but included only 4- & 7-year follow up [5]. The idea is similar to creation of an atrial level shunt, but has the benefit of providing only lower body desaturation while the upper body continues to receive fully oxygenated blood with a lower risk of embolism to the brain.

Dr Baruteau and colleagues in Europe have published the largest series of palliative Potts shunts in pediatric patients- 24 patients from 2003-2014 underwent the procedure (19 surgical shunts- 1 unidirectional valved shunt for infrasystemic pulmonary artery pressure, 5 transcatheter PDA stents) with 3 early deaths (12.5%) and all 21 survivors experiencing improvement in functional class [6]. In the six patients on intravenous epoprostenol therapy, all were able to be weaned off.

Drs Grady and Eghtesady report the largest North American experience at Washington University with 5 patients undergoing surgical Potts shunt- 4 Group 1 PAH and 1 Group 2 with left heart disease [7]. The first two patients were placed on ECMO in the operating room prior to the procedure and were successfully decannulated after shunt placement. Overall, 4 of 5 patients had clinical improvement; the patient who did not benefit from the procedure had subsystemic PA pressures and died 3 months post-operatively.

Finally, there is a small series of transcatheter Potts shunt creation in the absence of a PDA out of Boston with technical success in 3 of 4 patients (1 died during the procedure as a result of a hemothorax) with short term survival of only 2 patients [8]. This technique consists of needle
perforation of the descending aorta at the site of apposition the left pulmonary artery under fluoroscopic guidance to allow covered stent deployment between the vessels. At this time, it should probably be reserved for patients with drug refractory PAH and/or co-morbidities that are unfavorable for a surgical approach, and even then only in the hands of a very experienced pediatric interventional cardiologist.

Given the limited experience in pediatrics, Potts shunt may be considered as destination therapy or bridge to transplant based on the small aforementioned series in the European Paediatric Pulmonary Vascular Disease Network treatment consensus statement (Class IIb, Level of Evidence C – same class, evidence as atrial septostomy) [9]. Potts shunt is not included as a therapeutic option in the American Heart Association and American Thoracic Society guidelines recently published in Circulation although atrial septostomy is recommended for patients with RV failure, recurrent syncope, or crises despite optimized medical management (Class I, Level of Evidence B) [10].

As Dr Potts was quoted as saying in an October 27th, 1961 edition of the Chicago Daily Tribune describing his technique, “Progress in pediatric surgery has been so recent that a thorough realization of what can be done for children has not yet filtered through the medical profession to parents.” This remains true today with new utilization of an old technique, one I’m sure Dr Potts would never have envisioned as he first thought of the procedure to relieve cyanosis. Although the goal remains the same- to improve the quality of life in pediatric patients with heart disease.

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

References:


Reducing the Burden of Parenteral Prostacyclin Therapy: The Totally Implantable Prostacyclin System

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As clinicians caring for patients with pulmonary arterial hypertension (PAH) we have all experienced the challenging situation in which a patient should ideally be treated with a parenteral prostacyclin for advanced symptoms but was not felt to be an appropriate candidate or declined to start prostacyclin therapy. The reasons for this are varied, including a history of non-compliance, an inability or unwillingness to maintain an access site and long-term infusion pump, or an unstable social situation.

In addition, in many patients, particularly young, active patients such as children and adolescents, there is sometimes a social stigma associated with carrying an infusion pump on a daily basis, and managing a parenteral prostacyclin can impact a patient’s ability to do their daily activities such as playing sports, showering and swimming. Lastly, for those already on parental agents, there is also a significant daily burden of maintaining their infusion site, need to frequently mix drug, and risk of infection with intravenous agents. In essence, caring for their pump and infusion site becomes a portion of daily life for patients on parenteral prostacyclins.

This has led to greater interest in the use of alternative forms of prostacyclin therapy such as inhaled and now oral prostacyclin analogs. However, for patients with advanced symptoms, current guidelines still recommend use of parenteral agents.

So what if we could alleviate the burden of managing an infusion site, changing cassettes and mixing drug? Could this have a significant impact upon the patient’s quality of life, satisfaction with prostacyclin therapy, and ultimately open up parenteral prostacyclin agents to a greater proportion of patients who actually warrant this therapy?

Recent results of a multicenter, prospective, single-arm, clinical trial (DelIVery for Pulmonary Arterial Hypertension) demonstrated the feasibility and clinical benefit of a novel implantable intravascular delivery system for continuous treprostinil which has potential to address this treatment gap and simplify the regimen for those patients already on IV treprostinil.

The implantable pump is placed in the abdomen and a catheter is connected to the infusion pump and then tunneled under the skin to the venous access site. Patients were typically discharged from the hospital 24 hours after implant and the pump was programmed to deliver a priming bolus followed by a continuous infusion of treprostinil from the pump reservoir. The pump refill process
takes approximately 15 minutes and occurred when the drug volume in the pump reservoir was low at an interval dependent on the patient dose (up to 12 weeks with an average refill interval of 47 days). In this cohort of 60 implanted subjects at ten study sites, the drug delivery system maintained therapeutic drug levels as postimplantation plasma treprostinil levels were highly correlated with baseline levels.

In this preliminary study there were no catheter-related bloodstream infections or occlusions. Six-catheter related complications occurred in five patients over a mean duration of use of 367 days and included three catheter dislocations, one episode of mechanical catheter damage, one pneumothorax, and one episode of venous stasis. The complication rate of 0.27 per 1,000 patient-days with the implantable delivery device was markedly lower than the pre-defined criteria of 2.5 complications per 1000 days with external delivery devices.

Patients spent 75% less time managing their delivery system (average 0.6 hours per week), including time spent traveling to and from, and in, the PAH clinic compared with the external system they used prior to implantation (average 2.5 hours per week). The use of this system maintained NYHA functional class and 6MWD and was associated with a higher rate of patient satisfaction.

For patients requiring parenteral prostacyclins the new implantable pump may present a viable alternative to a traditional intravenous or subcutaneous method of administration. To the patient, the implantable device is simplified and more convenient; there is less room for user error with a more automated delivery system and no cassette mixing. The absence of a transcutaneous outlet resulted in a marked reduction in catheter-related complications. The majority of patients reported either no change or better quality of life, likely related to both convenience and being able to do more regular activities without concern for infusion site complications.

This novel drug delivery approach appears to improve the safety of IV prostanoid delivery and patient quality of life and has the potential to expand the availability of parenteral prostacyclins to a greater number of patients.

Disclosure statement: The authors have no conflicts of interest to disclose.

References:

Switching Therapies for Pulmonary Arterial Hypertension and Challenges in Going from “Famine to Feast”

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Who would have thought that even a few short years ago we, as practitioners, would be relatively spoilt for choice in deciding which pulmonary vasodilator therapy we should select for our pulmonary hypertension patients? We certainly are far from the days of “calcium antagonism or bust” but recent years have seen the PH treatment paradigm further moved on to pressing and relevant questions such as whether to use upfront combination therapy and the how to integrate oral prostacyclin agents into our practices.

Perhaps one of the agents that can cause many PH care providers considerable pause is when, how and in which PAH patients to use the soluble guanylate cyclase (sGC) stimulator, riociguat. By means of introduction for the uninitiated, riociguat acts to induce vasodilation in smooth muscle by both sensitizing the sGC enzyme to endogenous nitric oxide (NO) and also by direct stimulation of the enzyme. The resultant vasodilation appears potent and results in significant decreases in pulmonary vascular resistance (PVR) [1] and concomitant increases in cardiac output (CO).

Indeed, the vasodilatory effects from riociguat appear significant enough that its combination with phosphodiesterase-5 inhibitors (PDE5i) such as sildenafil or tadalafil may result in significant symptomatic drops in systemic blood pressure [2]. This presents the practitioner with a binary option: PDE5i or riociguat, which to choose?

At ISHLT 2016, data from a single center experience converting PAH patients from PDE5i to riociguat showed there was a significant drop in PVR and increase in cardiac index (CI) of 0.4 L/min/m2 in patients switched from PDE5i to riociguat. The RESPITE study, which has completed enrollment and whose final results are soon to be published, was designed to answer the question of the efficacy of switching from PDE5i to riociguat in stable but persistently symptomatic PAH patients not on prostacyclin therapy. Stay tuned in the coming weeks!

Prostacyclin therapies have also evolved from the somewhat onerous, short half-life parenteral formulations of epoprostenol through to inhaled and now on to oral prostacyclin analogs, including the most recently FDA and Health Canada approved prostacyclin receptor agonist: selexipag. The GRIPHON study, recently published in the NEJM by Sitbon et al., looked almost exclusively at WHO Functional Class II-III who were already on non-prostacyclin based regimens for PAH and showed a marked positive difference in the primary composite endpoint of time to first morbidity/mortality event [4].

Again, patients and clinicians may indeed wonder about transitioning from inhaled or parenteral agents to newer oral therapies – especially in those felt to be at high risk of complications inherent
to intravenous or subcutaneous delivery of the drug. Although there are some anecdotal discussions and centre-specific protocols for the interconversion of prostacyclin formulations, there has yet to be a rigorously critiqued and widely accepted method for this process and certainly, most practitioners would advise caution in attempting this transition with the newest oral formulations. New data for the transition from inhaled treprostinil or selexipag should soon be available from the TRANSIT-1 study which has completed enrollment.

Ongoing collaboration will be crucial to the successful incorporation of all these therapies and also to the determination of their interchangeability. This is certainly true for any new drugs but especially for rare disease entities like PAH.

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

References:


As we learned from the tale of the tortoise and the hare, slow and steady wins the race. Patience, hard work, and tireless commitment to innovation and progress are the keys to success. Are we winning the race when it comes to the management of pulmonary arterial hypertension (PAH)? From one perspective, the management of PAH has come a long way since the development of prostacyclin therapy in the mid-1990s. We now have 14 FDA approved therapies, utilizing multiple delivery routes and targeting different molecular pathways. Yet, progress has been slow compared to other chronic conditions. For example, treatment for hepatitis C (HCV) and human immunodeficiency virus (HIV) have leapt ahead over the past few decades as a result of several breakthrough therapies. Today, HCV can be cured in most patients, and those with HIV are living for decades following their diagnosis. By comparison, the management of PAH seems to be at 3 kilometers into a 5K race.

Before exploring what we need to do to reach the finish line, let us first reflect on how far we have actually come. In 1995, PAH was a rapidly fatal disease, with calcium channel blockers, and anticoagulation forming the mainstays of therapy, and only a minority of patients satisfactorily responding. The dawn of prostacyclin therapy began with the approval of epoprostenol as a continuous intravenous (IV) infusion. For the first time, our patients had hope, and the race was on! It was not without limitations however, as the drug not only had to be kept cold due to its heat instability, but its short half-life also required that it be administered as continuous infusion via central venous catheter and infusion pump [1].

Seven years later, a slightly more convenient prostacyclin came to market. Compared to epoprostenol, treprostinil had a longer half-life, reducing the risk of a life-threatening medical emergency in the event of a sudden interruption in therapy. Treprostinil was also stable at room temperature and could be administered via IV or subcutaneous infusion.

In 2003, a breakthrough in formulation led to the development of iloprost, an inhaled prostacyclin stable at room temperature. Iloprost overcame several of the initial obstacles of prostacyclin therapy, mainly the need for central venous access or subcutaneous access, and had a theoretical benefit of direct drug delivery to the lungs. However, the short half-life of iloprost made it a challenge for patients to take, requiring 10-15-minute inhalations six to nine times daily. Development of the longer-acting inhaled treprostinil followed suit in 2009, adding to the armamentarium of prostacyclin therapy choices. As the addition of inhaled treprostinil to a
background oral therapy has been shown to be efficacious, the role of inhaled prostacyclin continues to evolve with the potential to transition patients from the intravenous or subcutaneous routes [2].

The pacesetter in PAH has always been development of an oral prostacyclin. An oral formulation would obviate many of the disadvantages of parenteral formulations, including risk of infection and pump failure, as well as improve convenience for the patient [3]. Road blocks to development included a high incidence of drug side effects and developing a tolerable dosing schedule. Clinicians remained optimistic about the possibility of oral prostacyclin therapy, which finally materialized in 2013, when an oral form of treprostinil was introduced. The efficacy in clinical trials was limited, especially when used in combination with PAH therapy, but the drug gave physicians something to work with and motivation for the tortoise to keep running the race.

Optimism of oral therapy continued with the recent results of selexipag, an oral selective prostacyclin IP receptor agonist, showing clinical benefits when used as a monotherapy or combination therapy with other oral PAH therapies [4]. However, the ultimate role of selexipag of in PAH management – whether selexipag can replace inhaled or parenteral prostacyclin therapy – remains to be seen.

How does the future look for prostacyclin therapy? Is a finish line in sight? The results of delivering subcutaneous treprostinil using a fully implantable programmable intravascular delivery system was recently published, showing reduced catheter-related complications and improved patient satisfaction [5].

The BEAT study, a Phase III trial, is currently recruiting participants to assess the efficacy and safety of adding the oral prostacyclin beraprost to inhaled treprostinil [6]. The combination of oral and inhaled prostacyclin has not been explored previously and may represent a more efficacious alternative to current management strategies.

Although prostacyclin formulations have improved in convenience over the past few decades, overall advancements in the management of PAH remain slow when compared to other disease states. However, we remain hopeful that novel agents in the pipeline, targeting novel pathways, will not only enhance the pace at which the care of patients with PAH will improve, but also ensure we reach the finish line.

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Living with an LVAD – My Father’s Journey

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In September of 2010, at age 70, my father was diagnosed with lymphoma. But before I introduce him as a patient, let me tell you about him as a person. My parents have now been married for 55 years and my dad was born in the house he still lives in. He had always been very healthy, strong, hard-working and robust - he could fix anything and he only missed work on extremely rare occasions. My dad loves to garden, hunt, and spend most of his day outside, no matter what the weather. His doctors have a nickname for him – Superman!

After the initial shock of learning about his diagnosis, we got down to business and dad went through chemotherapy treatment with good results. He insisted that the port be placed in his left arm so he could still shoot his bow. But then we got more bad news. As a result of the chemotherapy, his heart was damaged and he developed congestive heart failure. We were referred to the Heart Failure Clinic at Allegheny General Hospital in Pittsburgh. He was treated with medications first, but his condition deteriorated and he was started on a 24/7 infusion of Milrinone. This didn’t slow him down. He still hunted that whole season with the IV bag attached. We understood that this was a temporary fix and were introduced to the idea of placement of a Left Ventricular Assist Device (LVAD). We had never even heard of such a thing! But we researched and discussed it amongst ourselves and dad made up his mind to go for it. The LVAD was placed January 30, 2014 – a scary day for us! That day, we were all there – my Mom, Grandma (Dad’s mother who was 93 at the time), my two brothers, my sister and sister-in-law. The surgery went well and dad was discharged home.

I have to admit that learning to live with an LVAD was a huge adjustment. We had to switch my parents’ bedroom because he needed to be closer to the bathroom so at night he could get there when he was off battery and attached to the base. Dealing with the LVAD was a major change for everyone, but especially Dad. He wasn’t crazy about the bag used to carry the controller and batteries. We tried different vests, but what worked best was a fishing vest mom ordered. She removed a flap from the back and used it to sew pockets inside the front to hold the batteries. This makes it easier for Dad getting on and off the tractors and four-wheeler. One day shortly after Dad got home, I walked over to visit (I only live about 2 ½ miles away) and couldn’t find him. I assumed he and mom went somewhere, so decided I’d walk back home through the woods. That’s where I found Dad! They told him to walk, so he was walking! The LVAD had definitely changed Dad’s life. He was never one to be held back by anything, and this was a burden in the beginning. Now, it’s second nature and he has adapted very well. It certainly hasn’t slowed him down.
In May of 2014, Dad had his first stroke. He recovered pretty well, but a second stroke in July left him with left arm weakness and speech deficits. He knows what he wants to say, but struggles to find the right words. Although he got better with time, he hardly ever said my name again. Little things that you take for granted and don’t even think about are things you miss the most. There came a point he thought about giving up – he wanted the doctors to take the pump out. But by September, he decided he was going to find his love for life again. And he never looked back! His days were filled with mowing, gardening and hunting and he became a Superman all over again!

I feel the LVAD has made the quality of life better for my Dad. I give so much credit to my mother. She’s had to learn so many new things! At 74, she’s drawing his INR every week, adjusting his diet accordingly, keeps all of his appointments straight, takes him for chemo treatments and keeps smiling. It takes a “team” to deal with such drastic changes in life and they’ve been an amazing team for 55 years. I also give so much credit to all of Dad’s doctors and the LVAD Coordinators. We’ve bombarded them with questions and phone calls and they are absolutely fabulous. There are times his doctor texts me out of the blue just to ask how Dad’s doing. Just knowing that she’s thinking of him means the world to me. I know he’s not “just a medical record number”; he’s a person they care about. They truly are wonderful people.

Would I recommend the LVAD? I guess that would depend on the circumstances. Bridge to transplant – absolutely. Destination therapy (Dad’s case) – that depends on the person. It is definitely a lifestyle change. It’s high tech, it’s a pain to lug around and it’s scary. If you realize up front that it will be challenging and face it head on with all the resources that you have, it’s a great thing. For my Dad, I feel it has allowed him to continue to be active. He would never want to be bedridden, or even be confined to being inside. That’s just not who he is or how he would want to spend his life.

He has taught us so much through all of this. Through the cancer, the heart issues and strokes, he rarely voices a complaint. His faith has never wavered and I am so proud of him and so blessed to be his daughter. He is my dad – and he is Superman!

Robert is finishing his third year on the VAD. Over the months, he has bought us countless vegetables and flowers from his farm that he has grown. Even though I have told him I am a vegetarian, he sends me pictures from his deer hunts! His family has probably educated an entire farming county about the VAD by now. He has met with other patients contemplating a VAD and told them about his experiences honestly. But his lymphoma has metastasized now and he is enrolled in hospice. Probably the only hospice patient we know who still hunts! He is Superman, after all.

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Pain and Suffering, Without Belief

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“So, as an atheist, how do you explain and deal with pain and suffering?”

I asked my friend, Jon, for his thoughts, as part of my exploration into how we filter pain and suffering through faith and religion. I’ve known Jon since we were in college together, thirty-something years ago. He’s a palliative care physician in New York and daily navigates his way through pain and suffering. I’d like to say we were sitting in some downtown bar, but we were both driving to our respective homes and talking via mobile.

“Like, how do I justify pain and suffering? What does it mean?” He paused. “Pain and suffering just happen. I can’t do anything to stop it. Let me tell you what I do every day. I recently had a patient who had been in a vegetative state for over two years. He’d been this dynamic, brilliant, young guy in law school. If this guy had lived, he would’ve been another John Kennedy. Until, one day...he was just in the wrong place at the wrong time: totally freak accident. Now this guy, who couldn’t see me, talk to me, or acknowledge me, was my patient. Despite that, despite all that, I knew a lot about him. I’d come to know this guy from his parents’ stories about him, to the point where I really felt like I knew him. I even had a dream about him...walking and talking. Anyway, this couple’s son was failing and was now truly dying, and seeing his parents relate during the last months was...I hate to say it, and if you tell my wife I’ll deny it...I watched them relate to each other in a way that I’ve never come close to in my marriage. So when that couple lost their grown up son, I could only be present and allow them to feel the connection to their son through me.”

“My profession, my role, gets more difficult as I relate more to these patients and their lives. Having children definitely changed and impacted on my relationship with suffering. The son was about the same age as my eldest daughter, which made my job more difficult. It was excruciating to watch these parents suffer so much and, yes, die with their child. A part of them died when he did. Even though his consciousness had been gone for two years and all that was left was his body, it was still so painful. There are parents who justify a child’s death by saying it’s just ‘the next step in the journey,’ but I don’t think so. What kind of journey is that, anyway? If I lost one of my children the only solution for me would be death. I would not want to live.” He took a breath. “So when this young guy died, I thought, ‘there but for the grace of...’ Of what? Of nothing. There’s no good reason for pain and suffering. There’s no good that comes of it. There’s just suffering.”

He continued. “You spend your time as a transplant doc, modifying peoples’ life spans, altering the course of their disease, using extreme therapies to prolong life and hopefully the quality of life, and in pediatrics it’s often because the parents want you to. I do the polar opposite: I escort people to that last moment of consciousness, help them push their boat away from the shore, then stand and
wave good-bye. It’s often a choice my patients make. I have this 50 yr old guy with heart failure: treatable, but impeded by poverty and depression. It was all just too much. So, he decided to stop taking his meds and die in hospice. His wife can’t wrap her head around his choice but understands it and is hoping for him to die quickly. That’s pretty enlightened and she loves the guy a lot. At this point, her suffering is watching him suffer.”

“The thing that palliative care has taught me about pain and suffering is that people have a choice as to how they process the pain and suffering, and how they relate to their own impending death. My job is to develop a relationship with my patients that allows them to relate to pain and death in whatever way they want or need to. Palliative care is more about the relationships than it is about the medicine.”

“For me, as an atheist, there’s no meaning, no underlying greater good, no redemption of the soul that comes with pain, suffering and death. There’s no place to go to: no heaven, no hell or otherwise. It’s just a ‘black void’ that’s existed since six billion years before I was alive. There’s no before-life and no after-life. People can be good or bad, or just mediocre; in the end, we all go to the same black void.”

“I treat my patients like humans. I talk with them, have fun with them, bull shit with them. Whatever they want. Whatever they need, I’m open to helping facilitate. I give a lot of morphine, if they want it, and pass no judgment. There’s no excuse for pain. There should be no pain. I can’t treat or cure death but I can treat pain. I give a lot of morphine.”

“What we do as physicians is incredibly meaningful. We do make a difference day to day and we do have some power over life and death. Sometimes you get caught up in the weeds of it. But we have to remember that we’re there for the patients. In my profession, if a suffering patient with some terminal condition wants to die, that’s okay. I can’t get caught up in the legality or the ‘what will his family think or want,’ because it’s my patient’s choice. I give whatever they want: morphine, dilaudid, Ativan. Whatever it takes.”

“My father died of lung cancer in his seventies, about 25 years ago, now. Remember? My Dad…” I could hear him shaking his head at his recollections. “He did not go gently. He was in denial until the day he died. I regret that I kept rubbing his face in his inevitable death, in his disease. Every time he talked to me about getting better, or feeling better that day, or some new drug he wanted to try, or how he was going to redo the house, I’d pull back and tell him that he was wasting time he didn’t have, and that he’d be dead in a few months. I’m sorry I failed to encourage his state of denial as that’s where he wanted to be. I’m sorry I didn’t talk more with him about what his next trip would be or where we’d go or what we’d do. My father’s death showed me that my job is to figure out where a patient wants to be and help him get there. Even if it’s, ‘I’m going to stop eating tomorrow. How long will it take me to die? Will it hurt?’ or ‘If it weren’t for the pain, I’d feel pretty good. I think I’m gonna lick this and be around for another few years.’”

“Whatever my patients want from me, they get. None of us knows what’s right for people when they’re faced with constant, chronic suffering and impending death, but it’s my job to find out; I
need to know what’s right for them and give it to them. Even if it’s morphine, and the permission to stop eating and go.”

“I see us all as infinitely sad. We’re living on borrowed happiness. Time, life, is over so soon. Too soon.” He paused. “And it just keeps going on, without a plan, a reason, salvation, or a God. That’s it.”

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EDITOR’S CORNER: Enlightening Us on Pain and Suffering

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Health care providers in the ISHLT caring for patients suffering from various heart and lung conditions tend to and deal with many who live with disease, experience pain, suffer with medication side effects, cope with attachments to machines, and will eventually die. Protocols have been established focusing on either infection and rejection or bleeding and clotting. Another focus has been adhering to protocols and guiding patients to comply with prescribed regimens to improve survival and optimize outcomes. An important focus is the scientific study of problems ranging primary graft dysfunction, acute cellular and antibody mediated rejection, chronic allograft dysfunction, the various infections and their categorizations, malignancies and countless other known and unknown medical consequences after replacement therapies. Progress has been made through innovation with substantial improvements. However, do we truly know what it’s like to exist in such a reality as our patients do? Do we know how our patients live in such a state? How do they go on with the routine activities of daily living? How do their families live and deal with the many problems that can arise? What is our role in this process?

Another dimension of our responsibility, which is seemingly getting lost from our routines of trying to do what’s best, is the alleviation of suffering. Like anyone else, our patients over time are aging and must age gracefully. They are dying and must die with dignity. In the process, we will rarely cure yet sometimes relieve suffering but always help, care and guide our patients, especially when they need it. Do we need to specifically know what we are doing? We know more now than we did yesterday. This implies we can help and care for others without knowing or knowing less unless we didn’t care or help others before. Sometimes we can help and care using incorrect concepts. The knowledge most useful in our clinical endeavors is not necessarily the knowledge of disease, rejection or infection – for example. Franz Kafka’s, “A Country Doctor” taught us about a sense of duty and responsibility. Kafka’s famous quote – "To write prescriptions is easy, but to come to an understanding with people is hard” rings loudly today, especially when it comes to opioids for pain relief and especially within managing the patients of the ISHLT. Our focus is to come to an understanding with our patients. We do not want to move away from the personal experience of the sufferer, but objective science steers us away from such personal experiences. We have depersonalized our terminology. The ECMO patient in the ICU instead of the wife with IPF eating, bathing, walking, sleeping and going to the bathroom in the confines of 100 square feet for more than three weeks awaiting lung transplantation, with her distressed husband who hasn’t left her side. We all have heard about the meningitis case in room such and such or the PRES case in the step-down unit. Where’s the dignity when we type patients by disease? Studying the various Arts, including literature through fiction, short stories, poetry and plays; music and art help recapture the human side of illness and suffering can complete our responsibilities, duties and dedication to our patients.
Science, with its empirical knowledge and quest for truth, is and must be objective. The Arts emphasize the subjective and experiential testimonies. Experiences with illness and suffering have many issues that may be best explained by literature than to what is scientifically understood. It’s the relationship with patients and their families which evolves from a verbal and narrative relationship that relies on the Arts and literature. Instead of the science of it all, this relationship benefits more from a knowledge of short stories, fiction, poetry, music, theater and well, life. The knowledge of language could be just as useful in conducting and nurturing this relationship in a wise and successful manner because of the Arts. It becomes an affair of talking, hearing, listening and understanding. Art widens and deepens our lens and improves our dialogue to help us understand our patients. Art and literature provide us with valuable testimonies about the cultural and ideological notions that attend illness, pain, suffering and death. Literature and language illuminate our understanding. As a result, we have a more inclusive portrayal of the essential and peripheral details encompassing medicine and suffering with the life and death of patients. By reading literature, listening to music and watching plays and movies, we are given a larger framework to delve into our patients through repeated conversations about their suffering, their life and their death.

There is a great deal written in the Arts about pain and suffering. We can turn to great literary works and understand how those in pain can actually speak and share with us their suffering. By reading about sickness, suffering and death, as well as spending time with our patients, we will be given a better grasp of these difficult precincts of life. This will enable us to imagine a reality that we cannot afford to experience personally and an experiential view that science cannot provide, unless of course we have suffered with our own disease.

Has anyone ever lived to tell us what it was like to die? Since this is an impossibility, I think, let’s examine pain. Can we measure pain? Can we communicate the topics of pain and suffering? Can we understand how people feel? Can we explain the color green to anyone born blind or describe the sounds of a French horn, chimes, or cellos to those born deaf? Focusing on pain is difficult enough. The more articulate we are, the more descriptive we can be. Regarding pain, its perception is not the same in everyone. To help us understand this, there is a definitive study on pain and inflicting pain. Elaine Scarry’s, The Body in Pain, is a study of pain, a study of torture and a study of situations where the body is subjected to terrible abuse. She describes pain in terms of a geological metaphor. “When one hears about someone with physical pain, the events happening within the interior of that person’s body – may seem to have the remote character of some deep subterranean fact belonging to an invisible geography that however portentous has no reality, because it has not yet manifested itself on the visible surface of the earth.” When our patients have a headache, chest pain or back pain, we cannot see their disease, but we hear their words. We look for signs of what we interpret as distress. Through Scarry’s geological metaphor, she describes a landscape of a geological or seismographical event happening well beneath the earth that we cannot get to it. She links it to the way we “speak about the heavens, alternatively it seems as distant as the interstellar events referred to by scientists who speak to us of a not yet detectable mystery of an intergalactic scream.” This impinges directly with the way we deal with people suffering in pain.
She puts pain in terms of Descartes - “I think therefore I am” by rewriting it as “To have pain is to have certainty – the bedrock of reality.” For the observer, pain is elusive – hearing about pain is the primary model to have doubt of what it is. When one speaks of their own pain, it is effortlessly detected, grasped and understood. There is no mystery and there is no doubt. However, observers such as ourselves when evaluating patients in pain, may recognize that pain cannot be effortlessly detected, grasped or understood. It is easy and almost certain for us to be unaware, unattuned and not sensitized to the reality of our patient who may very well be suffering or in pain – even with our best intentions with so-called empathy. It is the person who is unequivocally in pain which may be the most obvious example of what it is to have certainty. In our assessments, pain is what simultaneously cannot be denied and cannot be confirmed. Different from the sciences, Art in some ways can shed light on our ability to make the pain of the sufferer – to put into Scarry’s words - “less unstateable, less unshareable and hopefully undeniable to the observer.” Art performs the service of enlightening us.

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