VINCENT’S HIDDEN SENSE:

In this issue of the Links, we are humored by contributions from Katie Watkins Dewey and Elizabeth Sarmiento on “Do These Genes Look Good On Me? Pharmacogenomics and Transplantation” and “The Pharmacology of Antibodies and Transplantation,” respectively. David Salerno and Douglas L. Jennings caution us to be phlegmatic as they discuss “Right Ventricular Dysfunction After Left Ventricular Assist Device Placement and Cardiac Transplantation: Take a Deep Breath.” Edward Horn and Amresh Raina channel a sanguine Shakespeare in their article “Amiodarone Exposure Prior to Heart Transplantation – Kind of a Big Deal or Much Ado About Nothing?” Thenappan Thenappan and Kurt Prins frighten us with “Evil Humors, the Right Ventricle, and Pulmonary Arterial Hypertension,” and Roberto Badagliacca turns night to day for melancholy in “Right Ventricular Reverse Remodeling – Impact of Combination Therapy...From Midnight Insomnia to Clinical Practice.” Enjoy!

Vincent Valentine, MD
Links Editor-in-Chief

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IN THE SPOTLIGHT:

Do These Genes Look Good On Me? Pharmacogenomics and Transplantation

Katie Watkins Dewey, PharmD, BCPS
UCSF Medical Center
San Francisco, CA, USA
Katherine.Dewey@ucsf.edu

In transplant, it is important to ensure the correct dose of medications for our patients since maintaining therapeutic levels of immunosuppression is critical to prevent rejection. Many factors play a role in managing immunosuppression, but how does a person’s genetics also impact the efficacy of medications? Is there a way to optimize drug therapy and personalize medication with pharmacogenetics? What is the clinical impact of finding out that a person is an “ultra-rapid metabolizer” of a medication?

The study of pharmacogenomics involves searching for targets in the genome that might influence drug responses. How effective a medication is or the likelihood of adverse effects may be driven by differences in alleles between individuals. Like shopping for the perfect fit of blue jeans, customizing medications based upon a person’s genetic makeup is important to preserve a transplanted organ. A common target to look at in pharmacogenomics is the variation of alleles of the Cytochrome (aka CYP) enzyme phenotype involved in the metabolism of many medications. Patients with different CYP phenotypes may be classified as “poor metabolizers,” “intermediate metabolizers,” “extensive metabolizers” or even “ultra-rapid metabolizers” depending upon whether they have “functioning” or “non-functioning” alleles. This terminology is meant to help understand how these variations impact drug metabolism, but can be confusing and difficult to implement in a clinical setting. To aid in interpreting the influence of these different scenarios, the Clinical Pharmacogenetics Implementation Consortium (CPIC) was developed to produce practical clinical guidelines based upon different levels of evidence [1]. These published guidelines can be helpful to determine clinical relevance of the patient’s genotypic variation and can provide a more practical way to adjust medications when metabolism may be playing a factor in our patients.

Calcineurin inhibitors are a mainstay of immunosuppression in transplant, yet fluctuations in drug dosing and metabolism are common among individuals. There are data to suggesting that some of the differences in tacrolimus dosing between individuals may be attributed to variances in the CYP3A5 phenotypes. These different phenotypes between individuals can affect the therapeutic dose of tacrolimus and ultimately alter the success of the graft. For example, initiating an extensive metabolizer of CYP3A5 on a standard dose of tacrolimus may lead to lower tacrolimus trough concentrations which could in turn increase the risk of rejection. For this particular patient, the CPIC guidelines suggest increasing the starting dose of tacrolimus by 1.5 to 2 times the typical starting dose to achieve therapeutic trough concentrations [2].
Another common cytochrome that may be important in transplantation is \textit{CPY2C19} since it plays a vital role in the metabolism of voriconazole and the proton pump inhibitor omeprazole. Previous studies have shown \textit{CYP2C19} poor metabolizers have voriconazole trough levels that can be up to four times higher predisposing the patient to adverse reactions. The CPIC does not provide a specific guideline for dose adjustment, but recommends initiating therapy at a lower dose or choosing an alternative agent that is not dependent upon \textit{CYP2C19} metabolism if possible [3]. The potential for under dosing voriconazole is also of concern in patients with aggressive fungal infections as this may lead to treatment failure. One study looking at 24 cystic fibrosis lung transplant recipients receiving voriconazole found that there was a higher under-dose rate in patients that were ultra-rapid metabolizers [4]. Understanding a patient’s phenotype before initiating voriconazole may be the key to preventing unnecessary adverse effects or treatment failures in our transplant patients.

It is also important to avoid oversimplifying clinical decisions based upon a single phenotype. Transplant patients receive a large number of medications that intricately interact with each other and may be metabolized by several cytochrome pathways. For instance, the type of proton pump inhibitor in combination with a patient’s \textit{CYP2C19} phenotype may play a role in tacrolimus metabolism. A study looking at 89 liver transplant patients found that in patients taking omeprazole, the tacrolimus concentration (adjusted for the dose) was higher in \textit{CYP2C19} poor metabolizers compared to extensive and intermediate metabolizers. Interestingly enough, this study did not find this difference in patients that were taking lansoprazole. The authors hypothesize that the differences seen with tacrolimus dose adjusted concentrations is due to the selection of the proton pump inhibitor omeprazole that undergoes metabolism via the \textit{CYP2C19} pathway [5].

Though pharmacogenomics may provide useful information for making medication adjustments, there are limitations to practically using this information in the clinical setting. Resources may be limited to genotype each individual, and there may be a delay in the return of the phenotype from the laboratory. There is also the potential problem of multiple gene involvement and the effect of other interacting medications. However, a few measures can be taken to best use pharmacogenomics. The frequencies of many of the CYP variations do have trends among races and this information can be used to obtain genotyping in select patient populations, especially if accompanied by unexplainable fluctuations in medications. Patients with treatment failure or adverse effects may also benefit from genotyping in addition to analyzing medication levels.

Refinement of dosing is the goal to prevent unnecessary adverse effects and optimize efficacy. As a clinician, it is valuable to understand that pharmacogenomic influences are an additional consideration to think of in our patients. As this field grows, my hope is that the recommendations become more precise as important genes and polymorphisms are identified and the pharmacogenetics are continued to be studied in clinical trials. In the meantime, for questions with respect to drug metabolism you can always reference the list of guidelines that the CPIC maintains online or consult with your pharmacist!

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


FOCUSING ON PHARMACY & PHARMACOLOGY:

Right Ventricular Dysfunction After Left Ventricular Assist Device Placement and Cardiac Transplantation - Take a Deep Breath

David Salerno, PharmD

Douglas L. Jennings, PharmD, FAHA, FACC
Doug.Jennings.pharmd@gmail.com
New York Presbyterian Hospital
New York, NY, USA

Right ventricular failure (RVF) after heart transplant (HT) or implantation of a continuous-flow left ventricular assist device (CF-LVAD) is associated with significant post-operative morbidity and mortality [1,2]. Estimates of RVF after CF-LVAD implantation and HF have been as high as 45% [3,4]. In addition to non-pharmacological modalities and intravenous vasodilators, inhaled pulmonary vasodilators are a unique treatment option aimed at minimizing systemic absorption by delivering therapy directly to the pulmonary vasculature. No formal guidelines endorse agent selection, dosing or administration of inhaled pulmonary vasodilators post-LVAD or HT.

Even small increases in RV afterload secondary to rising pulmonary pressures can contribute to RVF [5,6]. RV function may worsen early after CF-LVAD implantation secondary to excessive unloading of the LV by the device. After HT, ischemia and reperfusion injury associated with organ preservation, cold ischemia time as well as elevated pulmonary pressures contribute to a weaker RVF [4,7,8].

Inhaled pulmonary vasodilators are primarily administered via endotracheal tube during mechanical ventilation. Inhaled administration presents several challenges: variability introduced by administration setup, nebulizer type utilized for aerosolization, mechanical ventilator mode and dosage form. Below are a summary of the agents available:

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of Action</th>
<th>Common Doses</th>
<th>Notes</th>
</tr>
</thead>
</table>
| Inhaled nitric oxide | Activates intracellular guanylyl cyclase, which increases concentrations of cyclic guanosine 3’5’-monophosphate | 1 to 20 parts per million via continuous inhalation | • Very short half-life  
• Can cause methemoglobinemia  
• Expensive  
• Limited systemic exposure |
<p>| Inhaled epoprostenol | Activates intracellular adenylate cyclase,              | 25 to 50 nanograms/kg/min                         | • Complicated administration               |</p>
<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Dosage</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhaled iloprost</td>
<td>Activates intracellular adenylate cyclase, which increases concentrations of cyclic adenosine monophosphate</td>
<td>5 to 10 mcg inhaled 6 to 9 times daily</td>
<td>Ease of administration</td>
<td>Potential for platelet inhibition and bleeding, potential hypotension</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>Patient must be intubated</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Less expensive</td>
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<td></td>
<td></td>
<td></td>
<td>Some systemic exposure</td>
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<td></td>
<td>Potential for platelet inhibition and bleeding</td>
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<td></td>
<td></td>
<td></td>
<td>Potential hypotension</td>
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</tr>
<tr>
<td>Inhaled milrinone</td>
<td>Inhibits phosphodiesterase III, which increases concentrations of cyclic adenosine monophosphate</td>
<td>6 mg/hour continuous inhalation</td>
<td>Less evidence of clinical efficacy</td>
<td>Patient must be intubated</td>
</tr>
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<td>Less expensive</td>
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<td>Systemic exposure</td>
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<td>Potential hypotension</td>
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<td>Arrhythmia</td>
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Dosing and administering inhaled pulmonary vasodilators can be cumbersome due to complicated dosing regimens or drug compatibility issues. For instance, a weight-based epoprostenol dosing strategy requires a dual infusion setup of reconstituted drug and normal saline due to lack of compatibility with epoprostenol. For this approach, one bottle of reconstituted epoprostenol (30,000 ng/mL) is infused through an IV pump, and a 500 mL bag of 0.9% normal saline is infused through a second, separate IV pump. The infusion rate of reconstituted epoprostenol is calculated based on
the desired dose (10-50 ng/kg/min based on ideal body weight), and infusion rate of saline is added to attain a combined total infusion rate of 8 mL/h (the aerosol output of the nebulizer).

A review of the current literature confirms that inhaled pulmonary vasodilator agents have been shown to decrease pulmonary artery pressure when used in the perioperative period of CF-LVAD implant or HT (see table below). However, the literature regarding the potential impact on clinical outcomes (e.g., survival or risk of developing RVF) is lacking with these medications.

<table>
<thead>
<tr>
<th>Study</th>
<th>Groups</th>
<th>Patients</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rajek et al. 2000</td>
<td>• Intravenous PGE1</td>
<td>• HT (n=34)</td>
<td>• Immediately after weaning PVR decreased by 50% in NO group vs. 10% in IV PGE1 group</td>
</tr>
<tr>
<td>(Randomized)</td>
<td>• Inhaled NO</td>
<td></td>
<td>• At 6 hours mPAP and PVR were similar between groups</td>
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<td></td>
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<td>• Weaning from CPB failed in no patients in NO group vs. 6 patients in IV PGE1 group</td>
</tr>
<tr>
<td>Ardehali et al. 2001</td>
<td>• Inhaled NO, withdrawal for 15 minutes</td>
<td>• HT (n=16)</td>
<td>• Discontinuation of NO for 15 minutes at 6 hours resulted in significant increase in mPAP, PVR, and RVSWI</td>
</tr>
<tr>
<td>(retrospective)</td>
<td>• Historical control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macdonald et al. 1998</td>
<td>• Inhaled NO, with withdrawal at 24 hours</td>
<td>• CF-LVAD (n=7)</td>
<td>• Withdrawal at 24 hours associated with rise in transpulmonary gradient and PVR</td>
</tr>
<tr>
<td>Khan et al. 2009</td>
<td>• Inhaled NO</td>
<td>• HT and lung transplant recipients (n=25)</td>
<td>• Both agents reduced mPAP, CVP, and improved mixed venous oxygen saturations</td>
</tr>
<tr>
<td></td>
<td>• Inhaled epoprostenol</td>
<td></td>
<td>• At 6-hr crossover, no differences in pulmonary pressures or systemic blood pressure</td>
</tr>
<tr>
<td>Theodoraki et al. 2006</td>
<td>• Inhaled iloprost</td>
<td>• HT (n=8)</td>
<td>• Iloprost decreased transpulmonary gradient, mPAP, and PVR</td>
</tr>
<tr>
<td>Haglund et al. 2015</td>
<td>• Inhaled milrinone</td>
<td>• CF-LVAD (n=10)</td>
<td>• mPAP decreased and cardiac index and right atrial pressures improved</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• No atrial arrhythmias or sustained hypotension observed</td>
</tr>
</tbody>
</table>

After review of the literature, we suggest that when RVF failure occurs in the setting of a normal pulmonary vascular resistance (PVR), first line therapy should be traditional intravenous inotropic
therapy. However, if the PVR is elevated (> 250 dynes/sec/cm$^5$ or 3 Wood units), or the patient has other evidence of a high RV afterload (i.e., a transpulmonary gradient > 12 mm Hg), then an inhaled pulmonary vasodilator is the preferred initial pharmacologic agent. Drug selection depends largely on the institution’s capacity to safely prepare and administer the medication, along with formulary considerations such as the high costs associated with inhaled iloprost and inhaled nitric oxide.

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References:
Amiodarone Exposure Prior to Heart Transplantation – Kind of a Big Deal or Much Ado About Nothing?

Edward Horn, PharmD., BCPS, BCCCP  
Edward.Horn@ahn.org

Amresh Raina, MD, FACC  
Araina@wpahs.org  
Allegheny General Hospital  
Pittsburgh, PA, USA

Amiodarone use in patients awaiting heart transplantation (OHTX) has been increasingly prevalent given the frequency of atrial fibrillation (AF) as well as ventricular tachyarrhythmias in our end stage heart failure population combined with the fact that only two antiarrhythmic agents – amiodarone and dofetilide – are recommended for use in patients with heart failure with reduced ejection fraction (HFrEF) [1]. Given the choice, an overwhelming majority of patients are given amiodarone for rhythm control in AF as seen in the AF-CHF trial (> 80% patients) [2,3]. Despite the practice of ubiquitous use, amiodarone’s pharmacokinetics present a challenge for patients that are awaiting OHTX. Amiodarone has a terminal half-life of nearly 6 weeks and a volume of distribution that allows it to saturate nearly every tissue in the human body. Amiodarone also inhibits CYP3A4, a major metabolic pathway for commonly used immunosuppressants, and can increase the QTc interval which can compound the effect of tacrolimus for the risk of torsades de pointes. Finally, amiodarone can cause sinus node dysfunction and bradycardia in patients early post-transplant, sometimes to the point that therapy is required for chronotropic incompetence. These circumstances can contribute to hemodynamic effects long after patients have discontinued therapy, including patients that have undergone OHTX. Examining this issue begs the question of is this truly something where practice should change?

Several retrospective analyses have evaluated the effect of amiodarone on a variety of outcomes after OHTX including mortality and delayed graft function. Several meta-analyses evaluating the available published data have noted several caveats when trying to answer this long-standing debate [4-6]:

- Do the potential immunomodulatory effects of amiodarone benefit OHTX patients early after transplant, thus negating negative hemodynamic consequences?
- Amiodarone dosing is not uniform in published data, thus limiting the heterogeneity of these reviews
- Does amiodarone use prior to transplant bias those treated due to an inherent increase in severity of illness?

The conclusions of these meta-analyses have been that despite their limitations, the available data show that amiodarone has not increased the risk of poor outcomes after OHTX for those treated prior
to transplant. However, a closer look at two recent publications may help tip the scales in deciding if this is truly a concerning issue.

A single center retrospective review was recently published JHLT by Wright et al evaluated the effect of amiodarone on severe primary graft dysfunction (PGD) in OHTX [7]. This study looked at 100 patients who were given amiodarone preoperatively to 169 patients not on amiodarone. An interesting caveat to this paper was the evaluation of cumulative dose effects of amiodarone in the amiodarone treated cohort. There were no statistically significant demographic differences between cohorts as well as perioperative and donor characteristics. Primary graft dysfunction occurred more often in patients that were given amiodarone versus no amiodarone (20% vs 5.3%; p < 0.001) although survival was not significantly different at 4 years (80.9% vs 84.5%; p = 0.097). Several interesting findings with respect to dose response were noted. The investigators evaluated ‘day-of-OHTX’ amiodarone dosing and found that each 100mg/day dose increase in this variable was associated with a 55% increase in the development of severe PGD. Additionally, when evaluating the cumulative 6-month dose total for amiodarone prior to OHTX, every 18,300 mg increase was associated with a 67% increase in severe PGD. This is the equivalent of adding 100mg per day for 6 months.

In an analysis published in JHLT earlier this year, Cooper et al evaluated the ISHLT Transplant Registry in the hopes of determining if amiodarone significantly increased the risk of death and other serious outcomes post-transplant [8]. This analysis investigated the issue in over 16,000 patients where roughly 30% were treated pre-operatively with amiodarone. Key findings in the demographics showed that amiodarone use has become more prevalent in recent years, and that patients that were given amiodarone were more likely to have left ventricular assist devices (LVAD) or intra-aortic balloon pumps as well as a history of sudden cardiac death or implantable pacemaker placed. In the propensity matched cohort, amiodarone use was associated with a higher risk of death, time on inotropes, length of stay and frequency of permanent pacemaker placement. This series is the largest available analysis in evaluating the effects of amiodarone on heart transplant-related outcomes.

In evaluating the current body of data, it appears that amiodarone is associated with adverse outcomes after OHTX; however, meta-analyses and smaller series have not borne out these findings [4-6]. In a clinical quandary as such, it would be prudent to exhibit judicious use of amiodarone in this patient population if at all possible merely due to the prolonged half-life of amiodarone its potential toxicities –both pre- and post-transplant. Like any medication, a true need should be demonstrated and alternatives explored given the long-term toxicity profile that exists – somewhere between being a big deal and completely ignoring amiodarone is where we currently lie.

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

References:


FOCUSING ON PULMONARY HYPERTENSION:

Right Ventricular Reverse Remodeling – Impact of Combination Therapy...From Midnight Insomnia to Clinical Practice

Roberto Badagliacca, MD, PhD
University of Rome Sapienza
Rome, Italy
Roberto.Badagliacca@uniroma1.it

Back to home after summertime, trying to induce sleep at night by looking at art online, I’ve been delighted by Magritte’s Les Amants. Frustrated desires are a common theme in René Magritte’s work. Here, a light veil prevents the intimate embrace between two lovers, transforming an act of passion into one of isolation and frustration. My drowsy mind immediately jumped to the tight association between pulmonary arterial hypertension (PAH) and the right ventricle (RV), where both untiring efforts on one side and hesitation on the other side have characterized the last two decades of research activities and debates. Many clinicians have been involved in the difficult task of facing the transition from imaging RV pathophysiology to its implementation and utilization in clinical practice. However, I believe we are no more than glimpsing at the tip of the iceberg, as a growing body of evidence now supports the fundamental role of the RV in PAH and the importance of imaging techniques for patients’ risk assessments.

Recent studies clearly show that various therapeutic strategies may have different impacts on RV morphology and function [1,2]. Echocardiography and magnetic resonance imaging have both shown to be useful tools in clinical practice for patient evaluation describing RV morphologic and functional characteristics and their changes during follow-up. Trivial effects might be expected from oral monotherapy, while increasing effects are achieved with more aggressive approaches, as upfront double oral combination and parenteral prostanoids plus oral drugs, potentially leading to RV reverse remodeling in a similar fashion to what has been clearly established with left ventricular systolic heart failure and disease modifying therapies. Further evidence [2] seems to support the concept that RV reverse remodeling is the driven mechanism to achieve patients’ clinical improvements more consistent with a low risk profile, as highlighted by international guidelines [3].

Nevertheless, some clinicians and researchers may still be aware that these interesting findings need to be validated by more robust, multi-centre studies and may have no better maxim for guiding the interpretation of the results in this setting than “look, but don’t touch.”

For this reason, I could be considered ingenious as Magritte was. It seems that all who see his painting are interested in the veils covering the faces of the main figures, instead of feeling the frustration of the two lovers. On the other hand, we may continue to chase multi-centre studies that will hardly come to life in recognizing the importance of RV imaging evaluation in PAH without hearing the shout behind current findings, thereby reflecting the feelings of established clinical practice.
After all, as with art, science is supposed to be inspirational, controversial, provocative and everything in between. Imaging evaluation of the RV is, in my opinion, one such painting that intrigues and provokes thought, leading to amazing findings, that like real gems lie just below the surface, hidden from view waiting to be unearthed.

Hopefully, no one will ever criticize the effectiveness of parachutes in saving lives because they have not been subjected to rigorous evaluation by using randomized controlled trials [4].

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

References:
Evil Humors, the Right Ventricle, and Pulmonary Arterial Hypertension

Kurt Prins, MD, PhD
prin0088@umn.edu

Thenappan Thenappan, MD
tthenapp@umn.edu
University of Minnesota Medical School
Minneapolis, MN, USA

Medieval medicine was based on the theory that four humors: black bile, phlegm, blood and yellow bile had to be balanced for the body to function properly and imbalance of these humors was the basis of human disease. Blood-letting was a treatment strategy implemented to restore humoral balance and remove evil humors from the body. Thankfully, our knowledge of human physiology is much more sophisticated and bloodletting, outside of polycythemia, is a treatment from the days of yore. However, inflammation may be the modern day evil humor that physicians must combat in multiple disease states.

Inflammation plays a key role in pulmonary arterial hypertension (PAH) disease development and progression [1]. At the microscopic level, histopathological analysis shows an increased number of multiple inflammatory cell types including T- and B-lymphocytes, macrophages, plasma cells, mast cells and dendritic cells into the pulmonary vasculature with strong evidence that these cells promote pulmonary vascular remodeling [1]. Moreover, adventitial fibroblast also play a central role in inflammation-mediated pulmonary vascular remodeling [2]. While this is more commonly observed in PAH associated with connective tissue disease, human immunodeficiency virus infection and schistosomiasis infection, it is also observed in idiopathic and heritable PAH. In addition, circulating levels of inflammatory cytokines (interleukin-1β, -2, -4, -6, -8, -10, -12p70 chemokine-CXC3L1, -CCL5, -CCL2, and leukotriene B4) are elevated in patients with PAH [3-5]. Elevated levels of circulating inflammatory cytokines are associated with increased mortality in PAH; however, we currently do not have a strong grasp on ways to combat inflammation in PAH as a way to alter the disease course [3, 6].

In our most recent work, we turned the spotlight of inflammation from the pulmonary vasculature to the right ventricle (RV) and investigated how one particular evil humor, interleukin-6 (IL6), is associated with RV dysfunction in PAH. This study was conducted because preclinical data demonstrated that IL6 has a negative inotropic effect on cardiomyocytes mediated through nitric oxide [7] and calcium mishandling [8]. The amount of IL6 mRNA in heart samples from patients who underwent cardiac transplant was inversely correlated with left ventricular ejection fraction [9]. Therefore, we investigated the relationship between serum IL6 and RV function in 40 PAH patients. We showed a negative logarithmic relationship between serum IL6 and RV function as quantified by echocardiography. Moreover, patients with higher IL6 levels had worse RV function as quantified by TAPSE and RV fractional area change, higher right atrial pressures and lower cardiac index despite no significant differences in mean pulmonary arterial pressure, pulmonary vascular resistance (PVR) and pulmonary arterial compliance (PAC) when compared to patients with lower IL6 levels. Finally, there was a significant association between IL6 and RV function even after adjusting for PVR and PAC on multivariable analysis [10]. While our findings are hypothesis generating, we were unable to determine if elevated levels of IL6 cause RV dysfunction, or if they are simply a consequence of RV
dysfunction in PAH patients. Therefore, more research is needed to further define the role of IL6 in RV dysfunction in PAH.

Moving forward, the PAH community will undoubtedly gain understanding of how the evil humors of inflammation play a role in PAH pathogenesis through ongoing clinical trials. Firstly, the effects of rituximab, a CD-20 monoclonal antibody, on PVR, six-minute walk test, time to clinical worsening and quality of life will be examined in patients with Systemic-Sclerosis associated PAH in a placebo-controlled trial (NCT01086540). Furthermore, the effects of tocilizumab, an IL6 receptor antagonist, on PVR, six-minute walk test and N-terminal pro-BNP will be examined in PAH patients in a single-armed study (NCT02676947). Finally, the Liberty trial, a phase 2 randomized, placebo-controlled, double-blind study, will evaluate the safety and the efficacy of leukotriene B4 inhibitor, Ubenimex, on PVR, exercise capacity and time to clinical worsening in patients with PAH on standard of care (NCT02664558). Hopefully, these three trials, in addition to other ongoing basic, translational and clinical research studies, will shed more light on how we can combat evil humors to improve outcomes in PAH.

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

References:
NEWS & ANNOUNCEMENTS:

Call for Nominations - Associate Director for Pediatric Lung Transplant ISHLT Transplant Registry

The ISHLT Transplant Registry seeks nominations for an Associate Director for Pediatric Lung Transplant to work closely with Dr. Samuel Goldfarb as he completes his term as Associate Director on the Transplant Registry Steering Committee.

For detailed information on the structure and responsibilities of the ISHLT Thoracic Transplant Registry Steering Committee please see the Registry web page.

If you are interested in this position, please submit a short statement of interest along with your CV to Megan Barrett (megan.barrett@ishlt.org) by October 25, 2017.

For any questions regarding this position, please contact Dr. Sam Goldfarb (goldfarb@email.chop.edu) or Josef Stehlik (josef.stehlik@hsc.utah.edu).
SPECIAL INTEREST:

The Pharmacology of Antibodies and Transplantation

Elizabeth Sarmiento
University Hospital Gregorio Marañón
Madrid, Spain

A major advance in the description of the chemical structure of antibodies was the discovery of the antibody light chain in the early 1960s by Gerald Edelman and Joseph Gally, who realized that these proteins were the same as the Bence-Jones protein described in 1845 by Henry Bence Jones. At around the same time, Rodney Porter characterized the antibody-binding (Fab) and antibody Fc regions of IgG. In 1972, the Nobel Prize in Physiology or Medicine was shared by Edelman and Porter for their discoveries on the chemical structure of antibodies.

Antibodies play a dual role in heart and lung transplantation. First, they are important mediators of humoral immunity against infection. At the majority of centers, we only base our assessment of CMV infection risks on donor and recipient anti-CMV IgG status. Some centers measure IgG levels to assess the risk of severe infection in both types of transplant. Second, antibodies are critical mediators of allograft immune responses. Antibody-mediated rejection is still a major barrier for long-term survival in both heart and lung recipients.

Antibodies are widely used in all kinds of immune-based methodologies that are necessary for monitoring transplant recipients. The Nobel Prize in Physiology or Medicine 1984 was awarded jointly to Niels K. Jerne, Georges J.F. Köhler and César Milstein "for theories concerning the specificity in development and control of the immune system and the discovery of the principle for production of monoclonal antibodies."

Monoclonal antibodies are particularly good diagnostic reagents because of their exquisite specificity. They generally show higher specificity than polyclonal antibody mixtures and are widely used in the monitoring of transplant recipients. Antibodies can be applied in a variety of assay formats to assess the presence or absence of a particular substance, the amount present and localization within tissues as well as the expression of lymphocyte markers. Antibody-based approaches are used to assess cytotoxic anti-HLA and non-HLA antibodies as well as in the assessment of lymphocyte subsets, humoral immunity factors, immunosuppressive drug levels and diagnosis of infections or antibody mediated rejection.

IgG and specific antimicrobial antibodies can be replaced using intravenous or subcutaneous immunoglobulins in patients with secondary antibody deficiency after heart or lung transplantation. Specific anti-CMV immunoglobulins are used in selected settings by some centers to prevent or treat CMV disease. High doses of intravenous immunoglobulin is a therapeutic strategy for desensitization in patients with high titer anti-HLA antibodies.
Monoclonal antibodies were first produced from the fusion of murine B lymphocytes and myeloma cells. Subsequent advances in technology allowed for humanized monoclonal antibodies, whose pharmacokinetic properties differ from those of murine monoclonal antibodies in humans. Current major therapeutic applications of monoclonal antibodies include cancer, chronic inflammatory disease, infection, and transplantation. In addition, monoclonal antibodies constitute the largest and fastest growing sector of the biological pharmaceutical industry. In heart and lung recipients, monoclonal antibodies are used for induction of immunosuppression and treatment of rejection or post-transplant lymphoproliferative disorders, as well as in desensitization protocols.

Owing to their mechanism of action, monoclonal antibodies are associated with a unique spectrum of immune-mediated efficacy mechanisms and adverse event profiles. The potential role of pharmacological monitoring of monoclonal antibody levels (pharmacokinetics) and for detection of the development of anti-drug antibodies is under evaluation in specific immune diseases. Several issues remain to be resolved with respect to defining precise indications, dosing, monitoring and optimal duration of therapy with these drugs.

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EDITOR’S CORNER:

From Physicians, Midwives, Apothecaries, Surgeons and Barbers to Bathmasters, Peddlers, Corn Doctors, Executioners, Knackers and Quacks for Health and Disease in the Enlightenment

Vincent Valentine, MD
University of Alabama Birmingham
Birmingham, AL, USA
Vvalentine@uabmc.edu

http://mikerendell.com/the-corn-doctor/

The last three Links’ Issues from the Editor’s Corner: 1) examined the scientific revolution which emerged from Natural Philosophy in the Renaissance (July 2017), 2) identified chemistry as a rational science distinguishing it from alchemy in the Enlightenment period (August 2017) and 3) looked at steps in developing and debunking theories through observation, experimentation and reasoning with a focused lens on the discovery of carbon dioxide and oxygen (September 2017). In this issue, we will adjust the lens on ourselves, *homo sapiens*, to gain a general understanding of health and disease from the 18th century with the bewildering array of medical healers and to understand how to maintain and repair our body when it gets out of balance. An important point of both medical knowledge and practice is that it was not confined by the law, nor did it necessarily follow social rankings to the extent one might expect.

Let’s start with a review of health and disease and how it was understood in the 18th century, then review the fascinating world of medical healers from 300 years ago. The theme is maintaining equilibrium or balance to recover from illness, the great leveler. Diseases does not discriminate and can affect anyone indiscriminately - from prince to pauper, master to slave and learned to unlearned, thus the best example of how equal we truly are. But before we move on any further, let’s digress and take note on how this month’s issue differs from the topics in the July, August and September issues of the Links. These topics require abstruse, acroamatic or esoteric knowledge limited to a very small and eclectic group of society. Abstruse by derivation means to push away, and connotes what has been pushed out of the realm of comprehension. Scholars and scientists use abstruse academic jargon to discuss esoteric or acroamatic subjects and ideas. Acroamatic is an abstruse synonym of esoteric. It originally referred to the specific writings of Aristotle addressed to his disciples as opposed to exoteric writings, which were intended for the populace. Don’t confuse exoteric with esoteric, the antonym of exoteric. In terms of knowledge about disease and healing in the 18th Century, this knowledge was exoteric extending across the haves and have-nots, noblemen and subordinates and magnates to the nobodies of society.

Enough of this inscrutable and recondite tangent, now back to the task at hand. An important observation to make is we cannot accurately describe healing practices of the 18th century if we
impose on them assumptions common to our own day; there is an accepted standard practice dominated by physicians, whose knowledge of health and disease differs drastically from the world of alternative practitioners. The understanding of health and disease was generally the same among physicians and non-clinical healers in the 18th century. This common understanding allowed the infirmed to go back and forth from one type of healer to another until he/she was satisfied, even when it involved crossing social boundaries. Healers were as common as their knowledge with people in both high and low social ranks.

So, what was the exoteric understanding of health and disease in the 18th Century? Health depended mainly on the notion of balance, an ancient theory that endured throughout the Medieval and Renaissance periods into the 18th century. Health required an equilibrium, for example, among the four humors, or fluids, in the body that corresponded to the four ancient elements of earth, wind, fire, and water. The corresponding humors were black bile, yellow bile, blood, and phlegm. If one was healthy, then these four humors were balanced. From ancient and medicinal physiology, the four humors or bodily fluids, were thought to determine a patient’s health or disposition by the relative proportions of these humors: blood, choler (yellow bile), melancholy (black bile) and phlegm. Blood, also known as the sanguine humor makes you upbeat, cheerful and confident, Choler, also known as yellow bile makes you passionate or irascible. Melancholy, also known as black bile makes you gloomy or dejected. Phlegm made you either cool and indifferent or dull and sluggish. Disease, then, arose when dysequilibrium occurred in the normal distribution of the humors. What’s quite evident and logical, when one is sick the solution is to restore the equilibrium. What’s not different from today is the actual first line of defense against disease and illness, prevention. That is, don’t get out of balance or off balance.

A modified form of humoralism persisted into the 18th century. The art of living a healthy life, of actively pursuing balance among factors we can control, fell under the concept of dietetics, which was understood in terms of “regimens” as opposed to the narrow view of today referring to food intake. The first step in observing these regimens of a healthy life is looking at the factors we can control. From the perspective of the 18th Century and back to antiquity, the things we can control were called the non-naturals, or things not given by nature. These controllables from three centuries ago are refreshingly no different from the logical regimens of healthy living today:

1. Fresh air
2. Food
3. Movement (exercise)
4. Sleep
5. Excretion
6. Passion

The “naturals” were the things beyond our control - this phrase frequently used today seems to have evolved from here – “we stabilize patients and manage ARDS, septic shock and renal failure.” We minimize harm and sometimes wait for the wisdom of the body to heal or let nature take its course, etc. With the evolution of science, we have a deeper understanding of natural law and can observe what’s predictable yet at times there’s not much we can do to change it. Therefore,
perhaps, *non-naturals* were things you can control, the regimens for good health. For obvious reasons, the first *non-naturals* is “fresh” air. Not polluted air, not air with foul odors, or with excessive carbon dioxide – obviously air enriched with oxygen, “pure” air – to refer you back to the prior issue. Foul air was not good for health.

Of all the *non-naturals*, Healers from the 18th Century paid particular attention to food and excretions. In terms of food, what you ate was important for your health. Mobility or exercise can certainly be controlled. It is your choice to do so or not. Couch potatoes or Jabba-the-hut activists or choosing to be physically active is your choice. It seems obvious what might be best for you. As with Nike – refer to thoughts on [Nice 2014 Links Issue](#), “just do it” or the old social adage of industry vs laziness. Laziness is hazardous to your health, which can bring us back to foul air, smoking can be hazardous to your health. Sleep is important, but what is more controllable is the “right” amount of sleep. If you cannot control your excretions then you’re going to be ill. Think about the madness of King George III and his worsening condition. The physicians would carefully and incessantly examine his excrements to determine the cause of his affliction. The illness of hampered evacuations prevailed frequently for many millennia as it still does today. The focus of balancing these non-naturals is rooted on the importance of *moderation*. Too much or perhaps too little of anything can kill you. Don’t allow a deficiency or excess of any of these *non-naturals*. If any of these are neglected and get out of balance, disease will surely set in. To maintain moderation, the most common remedies were blood-letting, purging and cupping. What’s crucial to realize here is that healers of all kinds agreed. This was the message reinforced by the increasing, popular literature that appeared in medicine during the 18th century written by physicians. It also marked the general views of all non-physician healers. However, we can distinguish physicians from non-physician healers but not according to the basic content of medical knowledge they possessed. The distinction was much more a social one.

The standards of a practicing physician today are drastically different from physicians and healers of the 18th Century. Today, physicians’ practices are governed by a rigid education curriculum and medical boards. In the past, there was no such distinction of physicians from the medical healers. Moreover, there was no way of separating the legitimate from the illegitimate. Simply a grant or license to practice was based on bias. The understanding to be scientific was just starting to emerge simply out of the enlightenment with the systemic study of disciplines such as medicine. The goal was to make all disciplines, including medicine, backed by science. Further, it took time for a consensus to emerge of what was meant by medicine to become a science and what being scientific meant, then the question of a practitioner of science. Before then, these terms were not in existence and only became possible with the professionalization of medicine.

Licensed healers, or officially sanctioned healers, were apothecaries, midwives and surgeons, all of whom had to complete an apprenticeship before securing approval from a *physicus*. Physicians had the right to practice internal medicine, but only apothecaries had the right to prepare and sell medicines. Physicians attended universities whereas shepherds and cowherds didn’t but were used by common man. There were various healers within the realm of physicians, from general practitioner at the base on up the pyramid to optimal medical faculty then personal physician to royalty. The life of most physicians was not easy and most had to initially treat for free. New
graduates who hung out a doctor shingle found things especially tough. A physician might become the district *physicus*. This position carried administrative duties of overseeing medical practice, but because the *physicus* answered both to a higher medical board *and* local political authorities, it was often a no-win situation. The *physicus* had to make sure all the rules were followed. Best if one could become a court physician or, even better, the personal physician of the duke or king. First class surgeons – did major surgeries, barber surgeons cut hair and performed cupping, heating a cup and applying it to the skin to create negative pressure and mobilize blood flow to promote healing. Unlicensed healers included an array of folks: bath masters, oculists, dentists, peddlers, executioners, knackers, corn doctors, wise women, cowherds, and so on. Authorities were granting permission to just about anyone. What about quacks? Quacks were those who poached on territory where they did not belong, undercutting the livelihood of others. Those with official sanction to practice resented the many healers who practiced without permission. Plenty of healers are saddled with this term. Physicians who dispensed medicine could be accused of quackery. One could be accused of quackery even if one had an official sanction in one area, but poached onto another’s territory. People who could pay tended to go to a physician, but most people went to whomever they thought might help, henceforth there remain many who harbor a distrust of physicians.

It wasn’t until the turn of the 19th century that the understanding of what it meant to be “scientific” began emerging. The transition to what would become known as “scientific medicine” would take time. It would be another half century before the physician was ever considered a scientist. Then, with the development of the germ theory of disease, the blending of medicine with experimental science became irresistible. It also involved the complicated question of the emergence of a practitioner of science.

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