The Road Toward Precision in PH: Personal Omics, Phenomics, and Wearables—Oh My!

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The keynote address of the 2018 Pulmonary Hypertension Association (PHA) Scientific Sessions given by Dr Roham Zamanian, "From Clinical Classification to Precision-Phenotyping: Envisioning Precision Medicine in Pulmonary Hypertension," was the perfect prelude to the final session of the symposium. In this session the speakers tackled the timely question: "Omics and Wearables in Pulmonary Hypertension: Are We There Yet?" Dr Michael Snyder of Stanford University described how longitudinal, integrative personal omics profiling that incorporate whole genome sequencing, multidimensional omics measurements, and data from wearables can be applied to: 1) determine what it means to be healthy; 2) potentially predict transitions from health to disease prior to symptom development; and 3) better monitor and treat chronic disease. Dr Anna Hemnes of Vanderbilt University shared promising preliminary data from the ongoing multicenter, collaborative PVDOMICS initiative (Redefining Pulmonary Hypertension through Pulmonary Vascular Disease Phenomics), funded by the National Heart, Lung and Blood Institute (NHLBI) and PHA. Finally, Dr Raymond Benza of the Allegheny Health Network shared intriguing pilot data on the safety and utility of an implantable hemodynamic monitoring device, the CardioMEMS™ HF system, in patients with advanced pulmonary arterial hypertension (PAH).

AN INTEGRATIVE PERSONAL OMICS PROFILE

As a leader in the field of functional genomics, proteomics, and personalized medicine, Dr Snyder provided an insightful perspective on how state-of-the-art omics technologies and big data can be applied to better define and more intelligently manage health. Dr Snyder started his talk by describing health as a product of an individual's genome and their "exposome." Examples of an individual's exposome include their lifestyle habits (eg, diet, exercise, stress) and environmental exposures such as toxins, allergens, and infectious pathogens. Based on this concept of genome + exposome = health (or disease), Dr Snyder's team began the ambitious endeavor of integrative personal omics profiling several years ago and is currently following more than 100 individuals.[1] Using multiple omics platforms (genome, epigenome, transcriptome, proteome including cytokines and autoantibodies, metabolome, and microbiome), wearable biosensors, clinical imaging, and questionnaires, billions of measurements are made over time in every subject (Figure 1). An individual's genome is sequenced once at baseline and then samples (blood, urine, stool, skin) are collected and tests completed every 3 months. When a participant experiences an illness like a viral infection or undergoes a medical procedure such as a colonoscopy, the frequency of sampling increases. The first goal of the study is to define what it means to be healthy in molecular terms at an individual level (not at a population level). In other words, a personalized baseline state of good health is determined and can serve as a custom comparator if a participant transitions to symptomatic disease. Another goal of the study is to identify the similarities and differences among healthy subjects and recognize how individual responses to illness compare to one another. Lastly, this study hopes to determine factors that affect the health of an individual and then utilize this information to both predict and manage disease.

Genomic sequencing identified clinically actionable DNA mutations in 12 out of the first 70 healthy subjects participating in the study. In other words, these individuals gained knowledge from their genome sequence, which either eventually manifested as a disease that they were previously unaware of or resulted in further screening tests to detect future disease earlier. A *BRCA1* mutation was detected in one subject,

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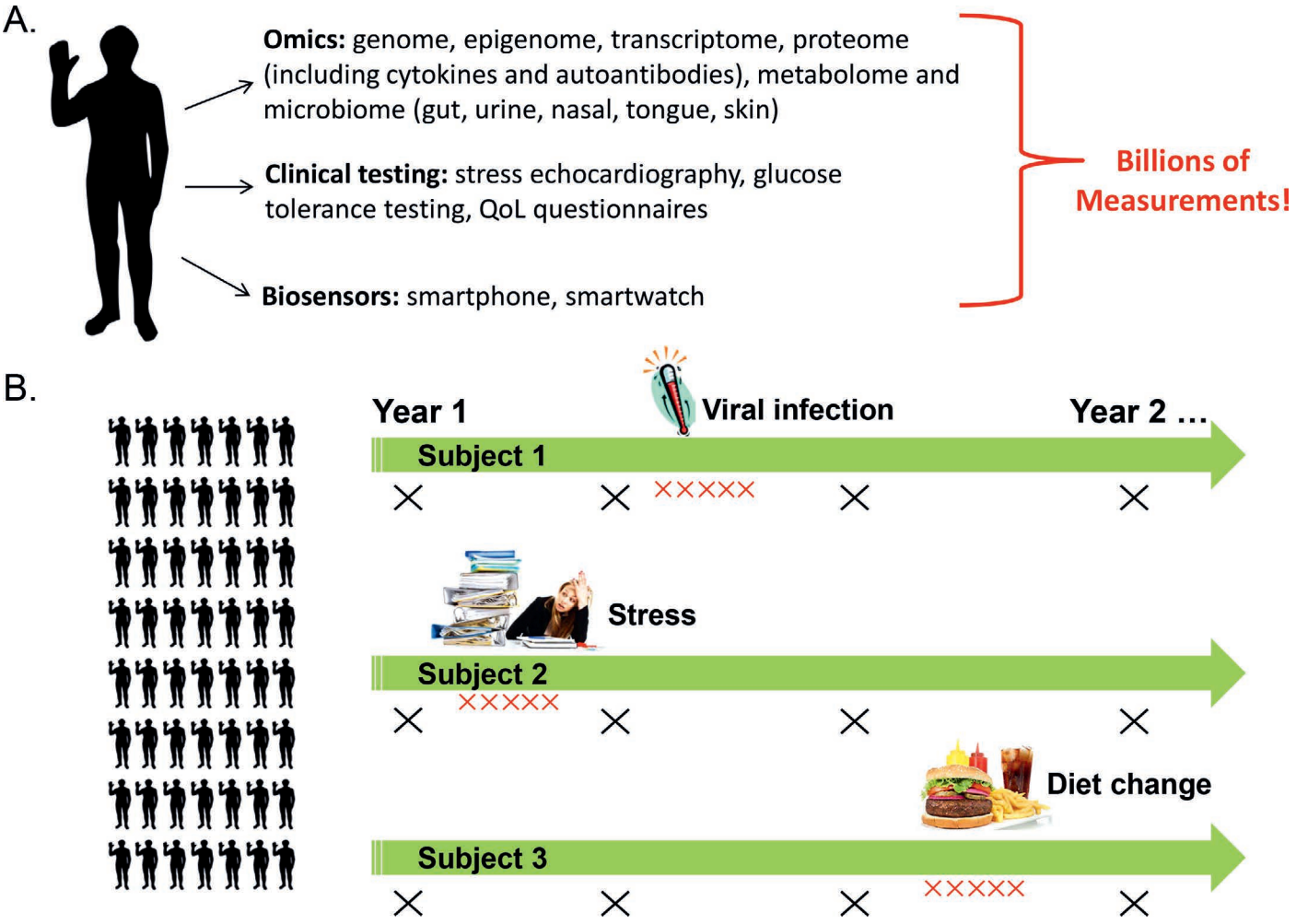

Figure 1: Integrative Personal Omics Profiling. **(A)** Each study participant undergoes deep-phenotyping including multidimensional omics assays, clinical testing, and biosensor monitoring. **(B)** Comprehensive assessments, as detailed in panel A, continue longitudinally in the cohort at regular intervals (black X), while more frequent testing is done during periods of illness or changes in health status (red X).

predisposing this individual to breast and ovarian cancer if they are female and breast, prostate, and pancreatic cancer if they are male. DNA sequencing in another individual revealed a pathogenic mutation in *RBM20,* which predisposes to the development of a dilated cardiomyopathy. The latter genomic results prompted a stress echocardiogram and medical therapy. Including those related to genomic variants, 45 major health discoveries were detected in individuals participating in this study (N=107; median age 53 years). One such condition, sleep apnea, was detected with a wearable biosensor (M.P. Snyder, PhD, unpublished data, 2018).

Wearable biosensors often measure routine physiological parameters, such as heart rate (HR), body temperature, and blood oxygen levels, that are also captured during an office visit with your health care provider. Yet infrequent sampling in a health care setting and comparisons to population-based normal values may be suboptimal for detecting and/or managing a patient's health.[2] Nor are various clinical parameters necessarily equitable across individuals of varying age, gender, fitness, and body habitus, but rather are more germane to the specific individual, particularly with regard to changes over time. Furthermore, some variables such as activity level cannot be measured during a routine office visit. Therefore, wearable biosensors are increasingly being investigated to determine their value in managing health and disease.[2] Li et al defined baseline personal patterns of resting HR, core body temperature, and activity level in 43 subjects using 7 wearable biosensors and investigated whether changes or deviations from baseline were relevant to health. Collectively, the 7 wearable devices used in the study recorded more than 250,000 measurements per day; thus, even subtle deviations from baseline could be identified. Based on a strong correlation between elevated heart rate and the onset of illness detected in 4 subjects in this study, an algorithm was developed to identify deviations in resting HR. The goal of the algorithm was to detect the onset of illness before a patient becomes overtly symptomatic simply by monitoring for changes in baseline heart rate. A future study using smartwatches and applying this

algorithm is planned in 1000 subjects to determine whether changes in resting HR can accurately predict when/if an individual will develop an illness before they are overtly symptomatic. With this example in mind, it is not farfetched to imagine a future in which wearable biosensor measurements are incorporated into a computational tool that predicts important health outcomes like "good/bad days," hospitalizations, or disease progression, in patients with chronic illness (eg, pulmonary hypertension).

Dr Snyder concluded with the metaphor of a patient's smartphone resembling a "command center" for their health, collecting copious amounts of multidimensional data that can be shared with their health care team. Finally, in the not so distant future, he hopes that genomic sequencing, omics measurements, and wearable biosensors can be seamlessly integrated into routine medical practice in order to better manage health by predicting risk, identifying disease early, and by monitoring and treating disease more effectively.

UPDATE ON THE NIH-NHLBI PVDOMICS PROJECT

In 2014, a new pulmonary vascular disease research initiative termed PVDOMICS was launched by the NHLBI Division of Lung Diseases.[3] PVDOMICS is a collaborative, multidisciplinary effort across 7 medical centers in the US. Cleveland Clinic is the data-coordinating center and the 6 clinical sites are Brigham and Women's Hospital, Columbia University/Cornell University, Johns Hopkins University, Mayo Clinic, University of Arizona, and Vanderbilt University. As a representative of the PVDOMICS team, Dr Anna Hemnes provided an overview of the study at the 2018 PHA Scientific Symposium. She described the different subject groups being investigated and presented demographic data on the nearly 700 patients enrolled to date as well as some preliminary metabolomics data. An overview of the study protocol was recently published, and a detailed description of the protocol methods are available in the online supplement.[4]

The goal of PVDOMICS is to perform deep phenotyping and endophenotyping across the World Health Organization (WHO) pulmonary hypertension (PH) subgroups 1-5 as well as comparator subjects with disease and healthy controls. Including a plan for comprehensive phenotyping of these additional disease comparator groups in the study protocol is quite unique and will be instrumental in downstream analyses. Some examples of the disease comparators include unaffected blood relatives of patients with heritable PAH, borderline PAH (21 < mean pulmonary artery pressure [mPAP] <25 mm Hg), patients with exercise-induced PAH (mPAP >30 mm Hg with exercise), connective tissue disease without PH (mPAP <25 mm Hg), left heart failure with isolated post-capillary PH, and interstitial lung disease without PH. The general hypothesis is that the integration of clinical metrics, both routine and more specialized testing, with detailed omics measures in the blood will elucidate previously unrecognized relationships at a molecular, cellular, and clinical level and potentially facilitate an updated classification system of pulmonary vascular disease (Figure 2).[4] As Dr Hemnes emphasized, at the heart of this exciting initiative is the hope that one day we will be able to make more precise and accurate diagnoses for our patients so that we can treat them with safer, more effective therapy.

The study inclusion criteria are intentionally broad. Subjects ≥18 years of age referred for right heart catheterization for either known or suspected pulmonary vascular disease are eligible if they are able to complete the protocol-related tests. Subjects who are on dialysis, are pregnant or nursing, or too ill to complete the required testing are excluded. Participating subjects undergo an in-depth clinical evaluation including blood collection (peripheral venous, pulmonary artery, and pulmonary capillary wedge samples), a body composition bioimpedance measurement, a 6-minute walk test, quality of life questionnaires, pulmonary function tests, noncontrast chest computed tomography (CT) imaging, a ventilation-perfusion scan, an overnight home sleep study, noninvasive cardiopulmonary exercise testing, a transthoracic echocardiogram, an electrocardiogram,

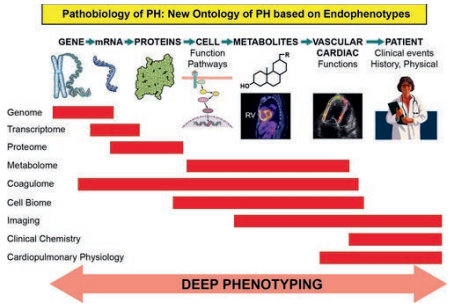

Figure 2: Omics Analysis Plan. Reprinted with permisison from Hemnes AR, Beck GJ, Newman JH, et al. PVDOMICS: A Multi-Center Study to Improve Understanding of Pulmonary Vascular Disease Through Phenomics. *Circ Res*. 2017;121(10):1136-1139. [https://www.ahajournals.org/doi/full/10.1161/CIRCRESAHA.117.311737]

and cardiac magnetic resonance imaging (MRI). Invasive hemodynamics are determined by right heart catheterization including provocative testing with 100% oxygen, inhaled nitric oxide, and acute volume loading (500 mL of warm normal saline infused over 5 minutes) each performed separately followed by repeat hemodynamics. Invasive cardiopulmonary exercise testing is performed instead of volume loading at centers with this capability. Following this thorough evaluation, subjects are classified according to the traditional WHO subtypes of PH. Study centers are targeting 25% incident cases within each PH subtype. Subjects with common mixed phenotypes (WHO Groups 2, 3 and WHO Groups 1, 3) will be included and classified as having both a primary and secondary diagnosis.

As of the end of June 2018, nearly 700 subjects have been enrolled in PVDOMICS. Target enrollment for the entire study is 1500 subjects, including WHO Groups 1-5 (n=1000), disease comparators (n=400), and healthy controls (n=100) (Table 1). The mean age of subjects enrolled to date is 56 (±15) years, two-thirds of the subjects are female due to the disproportionate number of WHO Group 1 subjects currently enrolled, and the mean body mass index is 30.1 (±7.7) kg/m^2 (Table 2). In subjects with PH, the average mPAP is 36.1 (±15.5) mm Hg at end-expiration and 35.7 (±15.1) mm Hg when using the computer-generated measure of mPAP. Over 20% of the PH subjects

Table 1. PVDOMICS Enrollment Update[a]

	Target Enrollment	Enrolled n, (% of target)
PH Subjects, WHO Group	**1000**	**439 (44)**
1	300	268 (89)
2	300	70 (23)
3	300	53 (18)
4	50	31 (62)
5	50	17 (34)
Healthy Controls	**100**	**45 (45)**
Disease Comparators, WHO Group	**400**	**183 (46)**
1[b]	120	48 (40)
2, mild or no PH[c]	125	22 (18)
2, moderate[d]		30 (24)
3, mild or no PH[e]	125	36 (29)
3, moderate[f]		35 (28)
4, mild or none[c]	30	12 (40)

Abbreviations: PH, pulmonary hypertension; WHO, World Health Organization

[a]Data current as of June 2018

[b]Includes relatives of heritable PAH patients, exercise-induced PAH and connective tissue disease without PH

[c]Defined as mPAP <25 mm Hg

[d]Defined as mPAP ≥25 mm Hg but isolated post-capillary PH

[e]Defined as mPAP <21 mm Hg

[f]Defined as 21 mm Hg < mPAP <25 mm Hg

Table 2. Characteristics of Subjects Enrolled in PVDOMICS[a]

	Mean (SD)	N	Missing Data
Age, years	56.1 (15.0)[b]	656	0
Female	54.9 (15.0)	417	0
Male	58.2 (14.8)	239	0
BMI, kg/m^2	30.1 (7.7)[b]	637	19
mPAP at end-expiration, mm Hg	36.1 (15.5)	460[c,d]	82
Computer-generated mPAP, mm Hg	35.7 (15.1)	536[c,d]	6

Abbreviations: mPAP, mean pulmonary artery pressure

[a]Data current as of June 2018

[b]Group means and SD are for the overall cohort including PH subjects, healthy controls and disease comparator groups

[c]Excludes healthy controls (n=44)

[d]Right heart catheterization results are not entered in the study database for a subset of patient participants (n=70)

were classified as having a mixed phenotype (ie, PH was attributed to both a primary and a secondary WHO Group classification).

In addition to the above demographic data, Dr Hemnes also shared preliminary metabolomics data from a subset of PVDOMICS subjects. Peripheral venous blood samples from healthy controls (n=16), subjects with idiopathic PAH (n=56), WHO Group 2 (n=9), and WHO Group 3 PH (n=14) were assayed using a complex lipid platform (≈1100 lipids measured per sample) and global metabolite platform (≈1000 metabolites measured per sample) from Metabolon®. Clustering subjects based on their global metabolomic profiles identified 5 distinct clusters that did not segregate according to WHO Group classification.

In conclusion, the PVDOMICS initiative offers a unique opportunity to identify the molecular underpinnings of pulmonary vascular disease unconstrained by traditional WHO clinical classifications. Furthermore, multidimensional endophenotype clustering may lead to a new classification system[5] and/or identify groups of patients that are likely to respond favorably to targeted therapeutic interventions in future clinical trials.

THE ROLE OF WEARABLE DEVICES IN PAH: THE CASE OF CARDIOMEMS™

Results from the REVEAL registry support a close link between morbidity and mortality where clinical worsening (defined as either worsening functional class, worsening 6-minute walk distance [6MWD], all-cause hospitalization, or initiation of parental prostacyclin therapy) was highly predictive of subsequent proximate mortality.[6] Therefore, we may improve survival if we identify patients early on the path to decompensation and intervene with therapy that prevents clinical worsening. Currently a number of risk assessment tools are available including the 2015 European Society of Cardiology/European Respiratory Society PH guidelines,[7] risk equations,[8,9] and a risk calculator.[10] It stands to reason, though, that we not only want to make accurate predictions, but we also want to make early, accurate predictions. In other words, worsening shortness of breath and decreased exercise tolerance (ie, worsening functional class) may accurately or reliably predict a subsequent hospitalization, but if there is no window to intervene and prevent the hospitalization, what is the value of the prediction? In contrast, if we could measure a variable or set of variables that occur several weeks or preferably several months prior to overt clinical worsening, this may offer the clinician the necessary therapeutic window to intervene and steer the patient clear of a future hospitalization. In the last presentation of the 2018 PHA Scientific Sessions, Dr

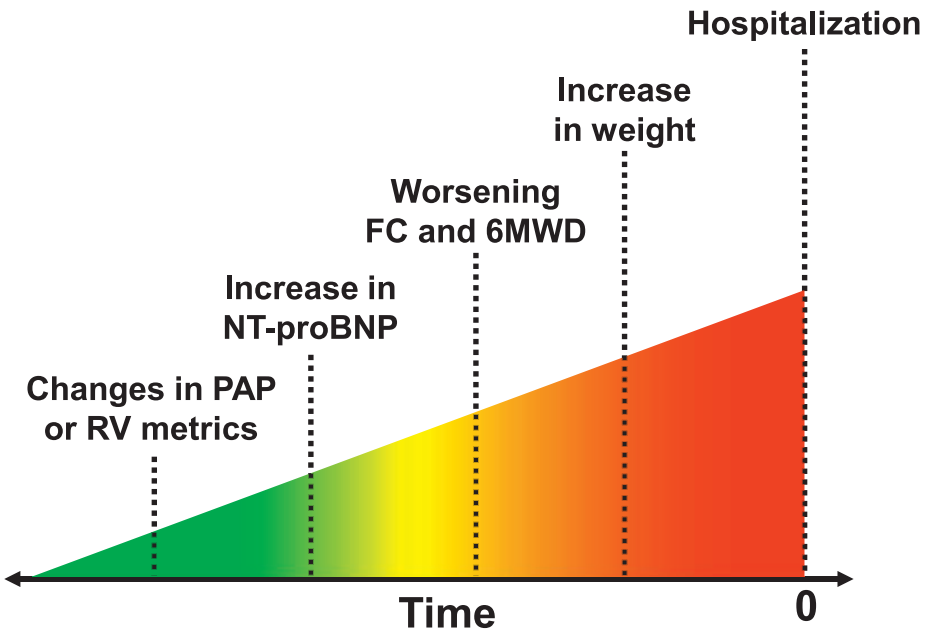

Figure 3: Clinical Timeline of Decompensated Right Heart Failure. Proposed schematic of the progression to decompensated right heart failure with the earliest signs being changes in hemodynamics and later signs being clinical symptoms. PAP, pulmonary artery pressure; RV, right ventricular; FC, functional class; 6MWD, 6-minute walk distance. Reprinted by permission from Springer. Adamson PB. Pathophysiology of the transition from chronic compensated and acute decompensated heart failure: New insights from continuous monitoring devices. *Curr Heart Fail Rep*. 2009;6:287-292.

Benza proposed that changes in pulmonary artery pressure (PAP), cardiac output, and ventriculovascular coupling detected continuously by an indwelling hemodynamic monitor such as the CardioMEMS™ HF System may offer an accurate and earlier prediction of clinical worsening in PAH patients. The underlying premise is that changes in hemodynamics represent early evidence that a patient is headed for clinical worsening (Figure 3).

The CardioMEMS™ system is an intravascular sensor that enables frequent hemodynamic assessments in the outpatient setting. Although much more invasive than a smartwatch, the CardioMEMS™ system is an example of what one might consider the "Cadillac" of biosensors. In contrast to the primarily static assessment of hemodynamics performed in the cardiac catheterization lab, an implantable device offers the opportunity to make serial measures in a variety of relevant clinical settings (eg, at rest, following exertion, and during sleep). The device is placed via right heart catheterization and a limited pulmonary angiogram is performed in order to identify a suitable (ie, straight) portion of the pulmonary artery for implantation. The Swan-Ganz catheter is then exchanged over a wire for the CardioMEMS™ deployment catheter (Figure 4). Once the device is implanted it typically occupies 10% of the artery lumen and undergoes endothelialization within 3 months. The sensor does not have leads or batteries. Nitinol wire loops extend from each end of the sensor and stabilize it at the implant location. The sensor is an airtight capsule containing an inductor coil and pressure-sensitive capacitor that create a resonant circuit at a specific frequency. Blood pressure affects resonant frequency so when PAP changes, the resonant frequency in the sensor changes. The sensor is calibrated using the measured hemodynamics at the time of implantation. In addition to monitoring PAPs, a mathematical algorithm is used to derive stroke volume from the PA waveform (Figure 4).

The CardioMEMS™ HF System is currently US Food and Drug Administration (FDA)-approved for use in New York Heart Association (NYHA) class III left heart failure patients, where it was shown to reduce heart failure–related hospitalizations.[11] Similarly, daily ambulatory hemodynamic monitoring reduced rates of hospitalization in the subset of patients with WHO Group 2 PH.[12] Based on these results, Dr Benza and his group received funding from the NHLBI to determine whether it is safe and feasible to use the CardioMEMS™ HF System in patients with severe PAH (NHLBI 268201400008C-0-0-1). This pilot study enrolled 24 moderate- to high-risk patients with a projected 1-year survival of 70% to 89% based on their REVEAL scores. Nearly two-thirds of the patients were on parental prostacyclin therapy and more than half were on triple therapy.

Although there were no immediate post-implantation complications, one patient died due to PA perforation during selective angiogram. This patient had complex congenital heart disease and multiple collateral vessels. Therefore, patient selection in any future studies should account for possible anatomic issues that might pose higher periprocedural risk. The remaining 23 patients did not experience any device-related safety issues at 1 year, and 7 patients have been evaluated up to 2 years post-implantation. Over the course of the study, improvements in a number of hemodynamic parameters were observed in the cohort including mPAP, cardiac output, stroke work, stroke volume index, total pulmonary resistance, compliance, and elastance. Improvements were also observed in functional class and quality of life assessment scores. However, since this was a pilot study, there was no usual care control group. Therefore, these improvements cannot be definitively attributed to monitoring by the CardioMEMS™ system.

In addition to evaluating safety and feasibility, the study also found that the device was compatible with cardiac MRI at 1.5 Tesla. Image quality was not affected by the device and the CardioMEMS™ signal was not degraded in the magnet. Furthermore, MRI-determined right ventricular (RV) volumes could be used in conjunction with CardioMEMS™-determined pressures to assess RV/PA coupling. In contrast to MRI, real-time data collection was hindered during 6-minute walk testing.

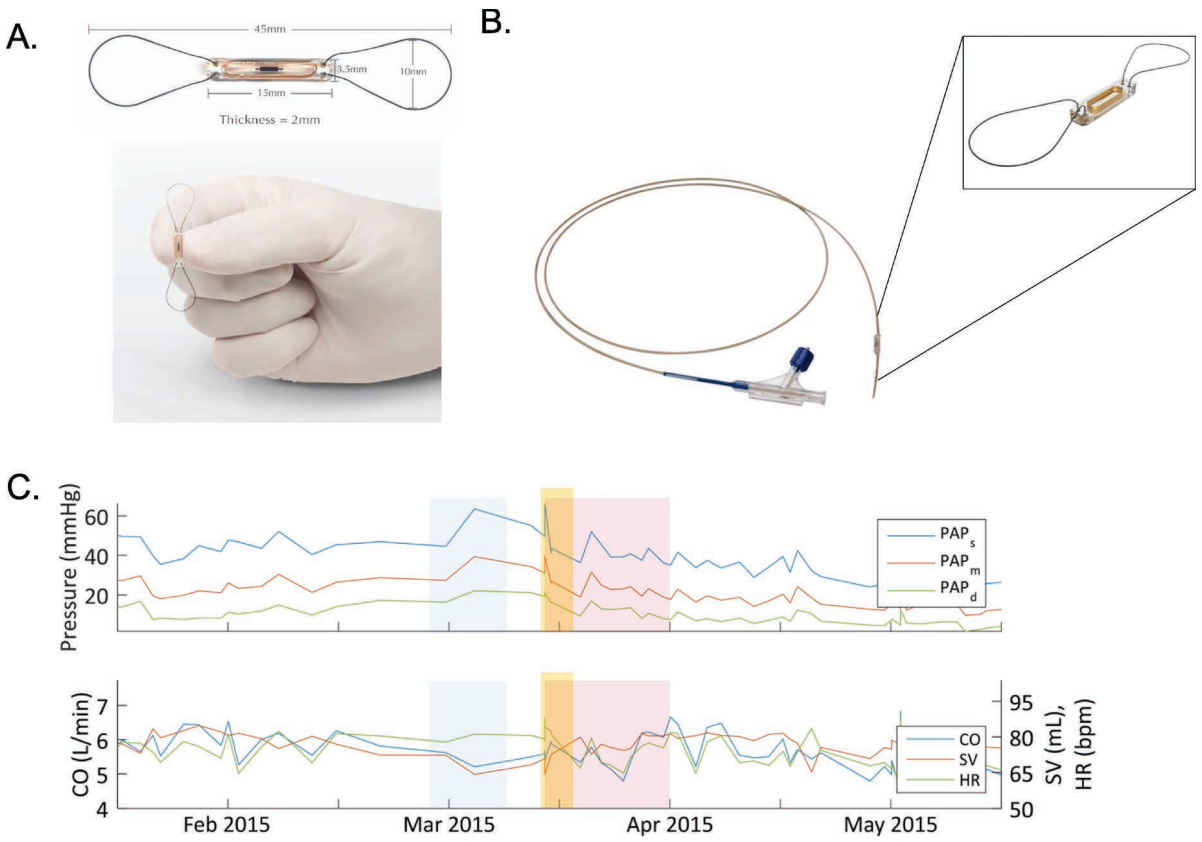

Figure 4: Ambulatory Hemodynamic Monitoring Using an Indwelling "Wearable" Biosensor. **(A)** Dimensions and relative size of the implantable CardioMEMS™ HF System. **(B)** The CardioMEMS™ HF System is loaded on the tip of a catheter for implantation. **(C)** Representative trends in pulmonary artery pressure (PAP), cardiac output (CO), and stroke volume (SV) over time in a patient with an indwelling CardioMEMS™ HF System. The blue-shaded rectangle corresponds to a period of time when this patient's hemodynamics worsened. The patient is subsequently hospitalization for right heart failure (orange rectangle) and receives appropriate therapy (red rectangle). PAP_s, pulmonary artery systolic pressure; PAP_d, pulmonary artery diastolic pressure; PAP_m, mean pulmonary artery pressure. CardioMEMS and St. Jude Medical are trademarks of St. Jude Medical, LLC or its related companies. Reproduced with permission of St. Jude Medical, ©2018. All rights reserved.

Pre- and immediately post-exercise hemodynamic assessments were feasible, but whether these measurements are more meaningful than resting hemodynamics remains unanswered.

In conclusion, Dr Benza presented interesting pilot data that supports further study of the safety and feasibility of the CardioMEMS™ HF System in selected PAH patients. In the future, in addition to comparing new invasive devices to traditional outpatient metrics used to manage PAH patients (eg, daily weights), these devices should also be compared to less invasive wearable biosensors.

CONCLUSION

Collectively Drs Snyder, Hemnes, and Benza provided those in attendance at the 2018 PHA Scientific Sessions with ample reason to be excited about what the future holds for precision medicine, omics, and wearables in the field of pulmonary vascular disease. One day we all hope to sit across from our patients and be able to offer them a more *precise* diagnosis and truly *personalized* care.

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