Impact of diabetes on survival and right ventricular compensation in pulmonary arterial hypertension

Levi Benson,¹ Evan L. Brittain,² Meredith E. Pugh,³ Eric D. Austin,⁴ Kelly Fox,⁴ Lisa Wheeler,³ Ivan M. Robbins,³ Anna R. Hemnes³

¹Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA; ²Division of Cardiology, Vanderbilt University Medical Center, Nashville, Tennessee, USA; ³Division of Allergy, Pulmonary and Critical Care Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA; ⁴Division of Pediatric Allergy, Immunology and Pulmonary Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA

Abstract: Insulin resistance is highly prevalent in pulmonary arterial hypertension (PAH) patients. However, the long-term impact of diabetes mellitus (DM) on survival in PAH is unclear. Insulin resistance and DM are associated with left ventricular steatosis and dysfunction, but whether the right ventricle (RV) might be affected by DM in PAH is unknown. We hypothesized that PAH patients with DM would have worse survival than PAH patients without DM and that this would be due to impaired RV compensation. From a large registry of PAH patients at our institution, we analyzed the effect of DM on survival in patients with idiopathic or heritable PAH. Clinical and hemodynamic differences were compared between PAH patients with DM and those without DM. Twenty-nine patients with DM and 84 without DM were included. Gender, body mass index, PAH type and duration, and 6-minute walk distance were similar between groups. PAH patients with DM had significantly lower survival at 10 years than PAH patients without DM. Right atrial pressure, pulmonary arterial pressure, and cardiac output did not differ significantly between the two groups. However, right ventricular stroke work index (RVSWI) was lower in the PAH DM group than in the no-DM patients. Among PAH patients with DM, patients who died had a lower RVSWI than survivors. In conclusion, survival in PAH patients with DM was reduced compared to that of patients without DM; impaired RV compensation may underlie this finding. Further study is needed to understand this effect.

Keywords: pulmonary hypertension, diabetes mellitus, right ventricle.

Pulm Circ 2014;4(2):311-318. DOI: 10.1086/675994.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare disease characterized by remodeling and obliteration of the pulmonary vasculature, which in turn leads to progressive right ventricular (RV) dysfunction and death.^{1,2} While there have been major advances in the knowledge of the pathogenesis^{3,4} and treatment⁵⁻⁷ of the disease, PAH still carries a very high rate of morbidity and mortality.⁸ Recent data have begun to highlight patient subpopulations at particularly high risk of death, including older patients, men, and those with connective tissue disease;⁹ however, the impact of comorbid conditions such as hyperlipidemia and diabetes mellitus (DM) on the prognosis of PAH is an

area of debate. If these common medical conditions are demonstrated to alter disease progression or survival, then aggressive therapy with already-approved medications may offer potential improvements in PAH-related outcomes.

Previous work has shown high rates of glucose intolerance and insulin resistance in patients with PAH.^{10,11} However, there are at present conflicting data on the impact of DM on survival in patients with pulmonary arterial hypertension.⁹⁻¹² Animal and cell culture models have suggested that insulin resistance plays a role in promotion of pulmonary vascular disease and is likely not just a bystander signifying end-stage PAH.¹³⁻¹⁵ Alternatively, insulin resistance

Address correspondence to Dr. Anna R. Hemnes, Division of Allergy, Pulmonary and Critical Care Medicine, T1218 Medical Center North, 1161 21st Avenue South, Nashville, TN 37232, USA. E-mail: anna.r.hemnes@vanderbilt.edu.

Submitted December 3, 2013; Accepted February 6, 2014; Electronically published April 15, 2014.

© 2014 by the Pulmonary Vascular Research Institute. All rights reserved. 2045-8932/2014/0402-0019. \$15.00.

and DM are associated with left ventricular steatosis and left heart dysfunction; the impact of these disorders of glucose homeostasis on RV function is unknown.

We hypothesized that idiopathic- and heritable-PAH (IPAH and HPAH, respectively) patients with DM would have worse survival than their PAH counterparts without DM. We used a large single-center registry of PAH patients to determine whether the presence of DM in PAH patients affects mortality. We further explored a potential negative impact of DM on RV compensation, using invasive hemodynamic measures.

METHODS

PAH patients

This study was approved by the Institutional Review Board at Vanderbilt University Medical Center (IRB no. 9401). We utilized data collected in a registry of PAH patients seen at our institution, the Vanderbilt University Pulmonary Hypertension Research Cohort (VPHRC), that has been previously described.^{16,17} Study data were collected and managed with the REDCap electronic data capture tool hosted at Vanderbilt University.¹⁸

For the purposes of our study, patients were included only if they carried a diagnosis of HPAH or IPAH.² PAH was diagnosed according to consensus criteria,⁶ including a mean pulmonary artery pressure of ≥ 25 mmHg and a pulmonary capillary wedge pressure (PWP) of ≤ 15 mmHg. IPAH or HPAH were diagnosed by experienced clinicians according to consensus guidelines.² Patients with HPAH had at least one confirmed family member within their bloodline with PAH. The VPHRC includes subjects not directly treated for clinical care at Vanderbilt University. For those subjects with PAH followed externally, diagnostic data were reviewed by clinicians at Vanderbilt University to confirm the diagnosis and type of PAH. To avoid confounding by treatment era, cases were restricted to those with diagnostic hemodynamic and clinical data between January 1, 1996 (when intravenous epoprostenol became commercially available), and March 1, 2011. Because this is an observational study, treatment decisions were at the discretion of the attending physician and not dictated by the study.

Demographic data, as well as data regarding patients' comorbidities—such as systemic hypertension and coronary artery disease (CAD)—at the time of PAH diagnosis, were also collected and recorded. For the purposes of our study, patients were defined as having systemic hypertension if they (1) had a blood pressure greater than 140/90 mmHg, (2) were on a Food and Drug Administration (FDA)–approved medication for hypertension, or (3) had a diagnosis of hypertension listed in the medical record.

Likewise, hyperlipidemia was recorded if patients were on a medication to treat hyperlipidemia or if hyperlipidemia was listed in their past medical history. Patients were defined as having CAD if they had undergone coronary artery bypass grafting or percutaneous coronary intervention or if they had CAD listed in their past medical history.

From the diagnostic right heart catheterization, heart rate, systemic systolic and diastolic blood pressures, right atrial pressure, pulmonary artery pressures, PWP, cardiac output, and cardiac index (CI) were recorded. Stroke volume, pulmonary vascular resistance (PVR), pulmonary capacitance (PC), and RV stroke work index (RVSWI) were calculated according to standard formulas.^{17,19,20}

DM definition

DM was defined as any of the following: random plasma glucose value of >200 mg/dL, self-reported diagnosis of DM, or treatment with an FDA-approved medication for DM. For the purposes of this analysis, patients with prediabetes, defined by glycosylated hemoglobin (HbA1c) of $\geq 6.0\%$,^{21,22} were considered to be in the DM group. Patients who met none of these criteria were defined as “no DM.”

Statistical analysis

Data are presented as mean $\pm$ standard deviation (SD) unless otherwise noted. Categorical variables were compared using the χ^2 or Fisher exact test according to specifications. Continuous variables were analyzed with unpaired, 2-tailed Student's *t* tests. Values for 6-minute walk distance (6MWD), PWP, CI, and PVR were all compared via *t* tests. The primary endpoint was all-cause mortality, as it was not always possible to determine an exact cause of death. Survival curves were constructed according to the Kaplan-Meier method, with differences compared by the Gehan-Breslow-Wilcoxon test. Cox proportional-hazards regression, stratified for presence or absence of DM, was used to determine predictors of death in the cohort. Logistic regression analysis was performed to examine prespecified predictors of death in the DM cohort (age, PVR, CI, and RVSWI). For all analyses, a *P* value of <0.05 was considered significant. All statistics were performed with GraphPad Prism and SPSS software (GraphPad Prism, ver. 5 for Mac, GraphPad Software, La Jolla, CA, www.graphpad.com; IBM SPSS Statistics, ver. 20 for Mac, IBM, Armonk, NY).

RESULTS

PAH characteristics

One hundred thirteen patients with IPAH or HPAH were identified from the registry. Of these, 29 were classified as

having DM and 84 as no DM. Demographic data for the two groups are presented in Table 1. The study population was predominantly female, with relatively equal distributions of IPAH and HPAH between the two groups. At diagnosis there were no differences in comorbidities of systemic hypertension, hyperlipidemia, or CAD between the two groups. As expected, HbA1c was elevated in the patients with DM ($P < 0.0001$). Of the patients with diabetes, 15 (52%) received a diagnosis of DM before their diagnosis of PAH and 14 (48%) afterward. Of the patients with DM, 8 were on no medical therapy. Of the 21 patients treated with antidiabetics, 15 were taking biguanides, one thiazolidinedione, one glucagon-like peptide agonist, 6 dipeptidyl peptidase-4 inhibitors, and 11 insulin. Combination therapy was used in 11 patients. HbA1c data showed a mean value of $7.3\% \pm 2.4\%$ in the diabetic patients. Although fasting glucose was not available in this cohort, the random plasma glucose value in the DM cohort was 136 ± 83 mg/dL.

There were no differences in PAH disease duration, treatment, or 6MWD between the patients with DM and those without (Table 2). Functional class was equally distributed between the two groups.

Diagnostic right heart catheterization did not demonstrate any differences in conventional hemodynamics between patients with DM and those without (Table 3). There

was a trend for higher right atrial pressure and lower PVR in the patients with diabetes, but this did not reach statistical significance.

Survival analysis

During a median follow-up of 76 months, there were 15 deaths overall, 7 in the group with DM and 8 in the no-DM group. Kaplan-Meier survival analysis was performed on the cohort and is shown in Figure 1. No patients underwent lung transplant. Despite the lack of observed differences in demographics or traditional risk factors such as 6MWD, hemodynamics, or therapy, there was a significantly lower 10-year survival among PAH patients with DM, compared to their counterparts without DM ($P = 0.04$).

RV function in diabetic PAH patients

Because traditional risk factors for mortality in PAH did not explain the observed mortality differences, we explored the hypothesis that RV dysfunction may underlie increased mortality in PAH patients with DM by examining RVSWI, a direct measure of RV work load (Fig. 2). In order to differentiate the effects of DM on the myocardium and the pulmonary vasculature, we examined PC as a composite measure of vascular resistance and elastic recoil. RVSWI was significantly lower in PAH patients with DM ($15.26 \pm$

Table 1. Pulmonary arterial hypertension (PAH) patient characteristics

	With DM ($n = 29$)	No DM ($n = 84$)	<i>P</i> value
Age at diagnosis, years	41.3 ± 14.3	45.8 ± 12.4	0.13
Female/male (% female)	24/5 (83)	62/22 (74)	0.33
PAH type			
Idiopathic	22 (76)	68 (81)	0.56
Heritable	7 (24)	16 (19)	
Type 2 DM	27 (93)		
Comorbidities			
Systemic hypertension	13 (45)	38 (45)	0.97
Hyperlipidemia	9 (31)	29 (35)	0.24
Coronary artery disease	2 (7)	2 (2)	0.26
BMI, kg/m ²	31.4 ± 6.8	29.8 ± 8.3	0.34
Systolic blood pressure, mmHg	125.3 ± 15.7	124.0 ± 19.2	0.80
Diastolic blood pressure, mmHg	76.0 ± 15.3	79.2 ± 15.2	0.48
HbA1c, % ^a	7.3 ± 2.4	5.6 ± 0.3	<0.001
Median follow-up, years	5.5	6.6	

Note: Data are no. (%) of patients unless otherwise noted. DM: diabetes mellitus; BMI: body mass index; HbA1c: glycosylated hemoglobin.

^a $n = 15$ for DM, 36 for No DM.

Table 2. Pulmonary arterial hypertension (PAH) patient treatment and disease severity

	With DM (<i>n</i> = 29)	No DM (<i>n</i> = 84)	<i>P</i> value
PAH medication			
Prostaglandin	13 (45)	34 (40)	0.69
PDE5I	11 (38)	17 (36)	0.83
ERA	8 (28)	24 (29)	0.92
Mean 6-minute walk distance $\pm$ SD, m	341.1 $\pm$ 164.3	367.9 $\pm$ 134.6	0.39
Mean duration $\pm$ SD, years	6.6 $\pm$ 5.1	7.1 $\pm$ 4.7	0.64
Functional class			
I	5 (17)	18 (21)	0.38
II	12 (42)	38 (45)	
III	11 (38)	27 (32)	
IV	1 (3)	1 (1)	

Note: Data are no. (%) of patients unless otherwise noted. DM: diabetes mellitus; PDE5I: phosphodiesterase-5 inhibitor; ERA: endothelin receptor antagonist.

5.63 g m/m²/beat) than in those without (18.13 $\pm$ 7.01 g m/m²/beat; *P* = 0.03), suggesting impaired RV compensation in PAH patients with DM. There was, however, no significant difference in PC between patients with DM and those without DM (*P* = 0.33).

In the diabetic PAH patients specifically, RVSWI was lower in nonsurvivors than in survivors (*P* = 0.03; Fig. 3). There was, however, no difference in PC between survivors and nonsurvivors with DM (Fig. 4). There were no significant differences in either RVSWI or PC between nondiabetic patients who survived and those who did not, although the event rate was lower in this population.

Table 3. Pulmonary arterial hypertension patient hemodynamics

	With DM (<i>n</i> = 28)	No DM (<i>n</i> = 72)	<i>P</i> value
RAP, mmHg	10.0 $\pm$ 6.7	7.7 $\pm$ 5.4	0.08
mPAP, mmHg	50.8 $\pm$ 10.1	54.9 $\pm$ 14.1	0.15
PA diastolic, mmHg	32.3 $\pm$ 7.5	36.6 $\pm$ 11.6	0.07
PWP, mmHg	7.5 $\pm$ 3.6	8.7 $\pm$ 3.4	0.12
CI, L/min/m ²	2.2 $\pm$ 0.5	2.2 $\pm$ 0.6	0.95
PVR, Wood units	10.3 $\pm$ 5.2	12.6 $\pm$ 6.0	0.09
Heart rate, bpm	79.8 $\pm$ 15.6	77.2 $\pm$ 12.3	0.48

Note: Data are means $\pm$ SD. DM: diabetes mellitus; RAP: right atrial pressure; mPAP: mean pulmonary artery pressure; PA diastolic: diastolic pulmonary artery pressure; PWP: pulmonary wedge pressure; CI: cardiac index; PVR: pulmonary vascular resistance.

On the basis of clinical experience and prior publications,^{8,23,24} we examined the following variables' association with survival among the diabetic PAH patients: age, PVR, CI, and RVSWI. Age and PVR were not associated with survival, but higher RVSWI and higher CI were favorably associated with survival in the diabetic patients (*P* = 0.019 and 0.023, respectively; Table 4).

DISCUSSION

In this study, we have demonstrated a significantly reduced 10-year survival in PAH patients with DM. Traditional markers of poor survival, such as demographics, reduced 6MWD, and standard hemodynamic markers of severity, were not different between PAH patients with diabetes and those without. Because RV function is a major determinant of survival in PAH, we examined RVSWI, an invasive hemodynamic measurement of RV workload. We found that RVSWI was lower in PAH patients with DM, which supports the hypothesis that RV function may be more impaired in the DM group.

Our data are in line with findings of other recent studies from our group and others that have investigated the interaction of DM and pulmonary vascular disease. We and others have demonstrated development and worsening of pulmonary vascular disease in mice after induction of insulin resistance.^{13,15} However, human data on the potential impact of DM on outcomes in patients with established PAH are less clear. Our prior data¹¹ showed a high prevalence of unrecognized glucose intolerance in PAH patients, but patients with known DM were excluded from that study analysis. Our present study showed no

Figure 1. Survival analysis. Kaplan-Meier survival curves in pulmonary arterial hypertension patients with diabetes mellitus (DM) and without diabetes mellitus (No DM). $P = 0.04$.

difference in short-term mortality between diabetic and nondiabetic PAH patients. Work by Zamanian and colleagues¹⁰ has shown that insulin resistance, as measured by the triglyceride/high-density lipoprotein (HDL) ratio, is more prevalent in the PAH population than in the general population and is associated with a lower 6-month event-free survival. Again, PAH patients with known DM were not included. Finally, large-scale registry studies such as REVEAL (Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management) did not collect information, such as triglyceride/HDL ratio or HbA1C, that might identify undiagnosed DM in PAH patients.²⁵ Although REVEAL did record data regarding comorbid DM and has recently suggested that DM may

negatively affect survival in PAH,¹² DM was not included in the REVEAL risk calculator,⁹ perhaps suggesting that a more sensitive marker of insulin resistance or DM may be needed to define the true effect of altered glucose homeostasis on PAH outcomes.

Because there are emerging data that insulin resistance and DM may negatively affect myocardial function^{26,27} and because no traditional survival factors appeared to differ between PAH patients with DM and those without DM, we explored a possible association of worse RV function in PAH patients with DM. RVSWI is a composite measure of RV workload that may better reflect RV compensation than cardiac output in certain clinical settings.²⁸⁻³² We have recently shown that RVSWI in PAH is closely associated with stroke volume, not heart rate, and thus likely is a metric of RV function in this disease.³³ It is interesting to note that both PAH populations, with and without DM, had supranormal values of RVSWI (normal range: 4–8 g m/m²/beat³⁴), reflecting necessary compensation for the increased load stress of PAH. However, we found that RVSWI was depressed in PAH patients with DM, compared to those without DM, and that higher RVSWI is associated with lower hazard of death in DM patients but not in PAH patients without DM. Further, in PAH patients with DM, RVSWI was lower in patients who died than in survivors. These data suggest that PAH patients with DM may be less able to compensate for pulmonary vascular disease-associated load stress. In contrast, we found no differences between PAH patients with and without DM in PC, a hemodynamic measure of the ability of the pulmonary vascular tree to dilate and store

Figure 2. Right ventricular hemodynamic compensation. Right ventricular stroke work index (RVSWI) and pulmonary capacitance in pulmonary arterial hypertension patients with diabetes mellitus (DM) and without diabetes mellitus (No DM). RVSWI was significantly lower in patients with DM (asterisk; $P = 0.03$). No differences were observed between the two groups in pulmonary capacitance ($P = 0.33$). $n = 28$ (DM), 72 (No DM).

Figure 3. Right ventricular stroke work index in survivors and nonsurvivors among pulmonary arterial hypertension patients with and without diabetes mellitus (DM). Asterisk indicates $P = 0.02$. $n = 22$ DM alive, 7 DM dead, 63 no-DM alive, 8 no-DM dead.

blood during RV systole and to then recoil and expel it during RV diastole that was previously shown to be an independent predictor of mortality in PAH.³⁵

There are limitations to our study. We did not include patients with connective tissue disease- or congenital heart disease-associated PAH, because these patients may be phenotypically different from IPAH or HPAH patients and DM may differentially affect survival in these conditions. We also stringently excluded patients with significant lung or left heart disease according to strict diagnostic criteria and thus lowered the total number of IPAH or HPAH patients that met our criteria.³⁶ This observational study incorporates data after diagnosis of PAH and thus cannot inform on the risk of PAH associated with DM. As the study was observational, we did not test the no-DM group for HbA1c or other markers of DM, and it is possible that some members of this group did have DM or insulin resistance. If true, however, this would bias toward the null hypothesis and thus strengthen our findings. We

did not collect data on the exact date of DM diagnosis in adequate numbers of patients to draw meaningful conclusions on the impact of duration of DM on PAH outcomes. Our study did not collect echocardiographic data on sufficient patients to translate our findings to noninvasive measures of RV function or to comment on possible effects of DM on left heart function, although all patients were required to have normal left ventricular ejection fraction in order to receive a diagnosis of PAH. There were relatively few events in the no-DM group, and cause of death is unknown for many, which limits our power for multivariate analysis. The mortality reported here in the no-DM group is relatively low but is likely similar to that experienced in other single-center registries with high rates of prostaglandin use³⁷ or favorable risk categories.⁹

In conclusion, survival in IPAH and HPAH patients with DM is lower than that in PAH patients without DM. Differences in RV compensation may underlie these mortality differences. The results of this study raise further

Figure 4. Pulmonary capacitance (PC) in survivors and nonsurvivors among pulmonary arterial hypertension patients with and without diabetes mellitus (DM and No-DM, respectively). No significant differences were found. $n = 21$ DM alive, 6 DM dead, 64 no-DM alive, 6 no-DM dead.

Table 4. Variables associated with survival in diabetic pulmonary arterial hypertension patients

Variable	OR	95% CI	P value
RVSWI	1.62	1.08–2.42	0.019
Age	1.07	0.98–1.161	0.134
PVR	1.08	0.86–1.36	0.513
Cardiac index	33.79	1.63–708.13	0.023

Note: OR: odds ratio; 95% CI: 95% confidence interval; RVSWI: right ventricular stroke work index; PVR: pulmonary vascular resistance.

questions, specifically, how insulin resistance and DM may have a detrimental effect directly on the right ventricle. Future basic science efforts should be directed at understanding the impact of insulin resistance on RV function.

ACKNOWLEDGMENTS

The contents are solely the responsibility of the authors and do not necessarily represent official views of the National Center for Advancing Translational Sciences or the National Institutes of Health.

Source of Support: This publication was supported by Clinical and Translational Science award UL1TR000445 from the National Center for Advancing Translational Sciences, K23 HL0987431 (EDA), 1 P01 HL 108800–01A1 (ARH, IMR, MEP), and an American College of Cardiology Foundation/Merck Fellowship in Cardiometabolic Disorders (ELB).

Conflict of Interest: None declared.

REFERENCES

- Farber HW, Loscalzo J. Pulmonary arterial hypertension. *N Engl J Med* 2004;351:1655–1665.
- Simonneau G, Robbins IM, Beghetti M, Channick RN, Delcroix M, Denton CP, Elliott CG, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2009;54(suppl.):S43–S54.
- Morrell NW, Adnot S, Archer SL, Dupuis J, Jones PL, MacLean MR, McMurtry IF, et al. Cellular and molecular basis of pulmonary arterial hypertension. *J Am Coll Cardiol* 2009;54(suppl.):S20–S31.
- Wilkins MR. Pulmonary hypertension: the science behind the disease spectrum. *Eur Respir Rev* 2012;21:19–26.
- Benedict N, Seybert A, Mathier MA. Evidence-based pharmacologic management of pulmonary arterial hypertension. *Clin Ther* 2007;29:2134–2153.
- Gal N, Hoeper MM, Humbert M, Torbicki A, Vachiry J-L, Barbera JA, Beghetti M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2009;30:2493–2537.
- Baliga RS, MacAllister RJ, Hobbs AJ. New perspectives for the treatment of pulmonary hypertension. *Br J Pharmacol* 2011;163:125–140.
- Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, Yaci A, et al. Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. *Circulation* 2010;122:156–163.
- Benza RL, Miller DP, Gomberg-Maitland M, Frantz RP, Foreman AJ, Coffey CS, Frost A, et al. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). *Circulation* 2010;122:164–172.
- Zamanian RT, Hansmann G, Snook S, Lilienfeld D, Rappaport KM, Reaven GM, Rabinovitch M, Doyle RL. Insulin resistance in pulmonary arterial hypertension. *Eur Respir J* 2009;33:318–324.
- Pugh ME, Robbins IM, Rice TW, West J, Newman JH, Hemnes AR. Unrecognized glucose intolerance is common in pulmonary arterial hypertension. *J Heart Lung Transplant* 2011;30:904–911.
- Poms AM, Turner M, Farber HW, Meltzer LA, McGoon MD. Comorbid conditions and outcomes in patients with pulmonary arterial hypertension: a REVEAL registry analysis. *Chest* 2013;144:169–176.
- Hansmann G, Wagner RA, Schellong S, de Jesus Perez VA, Urashima T, Wang L, Sheikh AY, Suen RS, Stewart DJ, Rabinovitch M. Pulmonary arterial hypertension is linked to insulin resistance and reversed by peroxisome proliferator-activated receptor- activation. *Circulation* 2007;115:1275–1284.
- Hansmann G, de Jesus Perez VA, Alastalo TP, Alvira CM, Guignabert C, Bekker JM, Schellong S, et al. An antiproliferative BMP-2/PPAR/apoE axis in human and murine SMCs and its role in pulmonary hypertension. *J Clin Invest* 2008;118:1846–1857.
- West J, Niswender KD, Johnson JA, Pugh ME, Gleaves L, Fessel JP, Hemnes AR. A potential role for insulin resistance in experimental pulmonary hypertension. *Eur Respir J* 2013;41:861–871.
- Larkin EK, Newman JH, Austin ED, Hemnes AR, Wheeler L, Robbins IM, West JD, Phillips JA, Hamid R, Loyd JE. Longitudinal analysis casts doubt on the presence of genetic anticipation in heritable pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2012;186:892–896.
- Brittain E, Pugh ME, Wheeler LA, Robbins IM, Loyd JE, Newman JH, Larkin EK, Austin ED, Hemnes AR. Shorter survival in familial versus idiopathic pulmonary arterial hypertension is associated with hemodynamic markers of impaired right ventricular function. *Pulm Circ* 2013;3:589–598.
- Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap): a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42:377–381.

19. Linehan JH, Dawson CA, Rickaby DA, Bronikowski TA. Pulmonary vascular compliance and viscoelasticity. *J Appl Physiol* 1986;61:1802–1814.
20. Barratt-Boyes BG, Wood EH. Cardiac output and related measurements and pressure values in the right heart and associated vessels, together with an analysis of the hemodynamic response to the inhalation of high oxygen mixtures in healthy subjects. *J Lab Clin Med* 1958;51:72–90.
21. Cowie CC, Rust KF, Byrd-Holt DD, Gregg EW, Ford ES, Geiss LS, Bainbridge KE, Fradkin JE. Prevalence of diabetes and high risk for diabetes using A1C criteria in the U.S. population in 1988–2006. *Diabetes Care* 2010;33:562–568.
22. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2010;33(suppl. 1):S62–S69.
23. Benza RL, Miller DP, Gomberg-Maitland M, Frantz RP, Foreman AJ, Coffey CS, Frost A, et al. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). *Circulation* 2010;122:164–172.
24. D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, Fishman AP, et al. Survival in patients with primary pulmonary hypertension: results from a national prospective registry. *Ann Intern Med* 1991;115:343–349.
25. Badesch DB, Raskob GE, Elliott CG, Krichman AM, Farber HW, Frost AE, Barst RJ, et al. Pulmonary arterial hypertension: baseline characteristics from the REVEAL Registry. *Chest* 2010;137:376–387.
26. Rutter MK, Parise H, Benjamin EJ, Levy D, Larson MG, Meigs JB, Nesto RW, Wilson PWF, Vasan RS. Impact of glucose intolerance and insulin resistance on cardiac structure and function: sex-related differences in the Framingham Heart Study. *Circulation* 2003;107:448–454.
27. Chokshi A, Drosatos K, Cheema FH, Ji R, Khawaja T, Yu S, Kato T, et al. Ventricular assist device implantation corrects myocardial lipotoxicity, reverses insulin resistance, and normalizes cardiac metabolism in patients with advanced heart failure. *Circulation* 2012;125:2844–2853.
28. Slaughter MS, Pagani FD, Rogers JG, Miller LW, Sun B, Russell SD, Starling RC, et al. Clinical management of continuous-flow left ventricular assist devices in advanced heart failure. *J Heart Lung Transplant* 2010;29(4 suppl.):S1–S39.
29. Ochiai Y, McCarthy PM, Smedira NG, Banbury MK, Navia JL, Feng J, Hsu AP, et al. Predictors of severe right ventricular failure after implantable left ventricular assist device insertion: analysis of 245 patients. *Circulation* 2002;106:1198–1202.
30. Mizushige K, Yao L, Noma T, Kiyomoto H, Yu Y, Hosomi N, Ohmori K, Matsuo H. Alteration in left ventricular diastolic filling and accumulation of myocardial collagen at insulin-resistant prediabetic stage of a type II diabetic rat model. *Circulation* 2000;101:899–907.
31. van Heerebeek L, Hamdani N, Handoko ML, Falcao-Pires I, Musters RJ, Kupreishvili K, Ijsselmuiden AJJ, et al. Diastolic stiffness of the failing diabetic heart: importance of fibrosis, advanced glycation end products, and myocyte resting tension. *Circulation* 2008;117:43–51.
32. Tuunanen H, Ukkonen H, Knuuti J. Myocardial fatty acid metabolism and cardiac performance in heart failure. *Curr Cardiol Rep* 2008;10:142–148.
33. Brittain E, Pugh M, Wheeler L, Robbins I, Loyd J, Newman J, Austin E, Hemnes A. Prostanoids but not oral therapies improve right ventricular function in pulmonary arterial hypertension. *J Am Coll Cardiol* 2013;61(suppl.):E2119.
34. Sturges DJ, Morgan TJ. Haemodynamic monitoring. In: Bernstein AD, Soni N, eds. *Oh's intensive care manual*. 6th ed. Philadelphia: Elsevier, 2008:105–122.
35. Mahapatra S, Nishimura RA, Sorajja P, Cha S, McGoon MD. Relationship of pulmonary arterial capacitance and mortality in idiopathic pulmonary arterial hypertension. *J Am Coll Cardiol* 2006;47:799–803.
36. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, Mathier MA, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association: developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. *J Am Coll Cardiol* 2009;53:1573–1619.
37. Sadushi-Koliçi R, Skoro-Sajer N, Zimmer D, Bonderman D, Schemper M, Klepetko W, Glatz J, Jakowitsch J, Lang IM. Long-term treatment, tolerability, and survival with subcutaneous treprostinil for severe pulmonary hypertension. *J Heart Lung Transplant* 2012;31:735–743.