Insulin Resistance and Pulmonary Arterial Hypertension

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Abstract

In view of the importance of insulin resistance (IR) and associated abnormalities in the genesis of cardiovascular disease (CVDz) it is reasonable to think IR could play a role in the pathogenesis and clinical course of pulmonary arterial hypertension (PAH). Lines of evidence which suggest this hypothesis are (1) the endothelial dysfunction characteristic of PAH is similar to that in cardiovascular and peripheral vascular disease, in which IR has been shown to play an important role; (2) obesity and low physical activity are clearly associated with insulin resistance; (3) the prevalence of obesity is increased in patients with pulmonary arterial hypertension; (4) PAH patients tend to be sedentary. In order to test this hypothesis we reviewed the clinical characteristics and fasting lipid profiles on a convenience cohort of 79 patients with PAH from the Stanford PH Database, excluding patients with a known history of liver disease, congenital heart disease (uncorrected) cancer, and diabetes. The average BMI of these patients was 29.6 kg/m2 (SD 8.4) and 56 patients (71%) were overweight or obese by conventional criteria. The average triglyceride/HDL ratio (TG/HDL) (a marker of insulin resistance when > 3) among all 79 patients was 3.1 (SD 1.8; range 0.8-10.2), consistent with an increased prevalence of insulin resistance. Thirty-four of the 79 patients (43%) had TG/HDL ratios greater than 3, indicating insulin resistance, while 39/79 or 36.7% had ratios of less than 2 and were insulin sensitive (IS). Furthermore IR patients appeared to be sicker as indicated by higher NYHA class III/IV (56% in IR group versus 48% in IS group) and a greater number of those on prostanoid therapy (50% in IR group versus 34% in IS group). We have demonstrated an increased prevalence of IR among a cohort of PAH patients. While the etiology of PAH is likely to be multi-factorial these results suggest that IR may represent an important contributing factor to disease development or disease progression, or both in PAH. If this hypothesis is true then treatment aimed at improving insulin resistance may have benefit for a large percentage of patients.

Introduction

Individuals who are insulin resistant (IR) and hyperinsulinemic are more likely to be hypertensive and have a dyslipidemia characterized by a high plasma triglyceride (TG) and low high-density lipoprotein cholesterol (HDL) concentration. They are also at increased risk for cardiovascular disease. IR is associated with various manifestations of endothelial dysfunction including increased adherence of mononuclear cells to endothelium, elevated plasma levels of PAI-1, elevated levels of adhesion molecules and elevated levels of ADMA, an endogenous inhibitor of nitric oxide synthase. Plasma concentrations of several markers of vascular inflammation, including white blood cells and C-reactive protein, are also increased in insulin resistant individuals. The strong link between insulin resistance and systemic vascular disease and endothelial dysfunction suggests that insulin resistance may also contribute to the vascular abnormalities which characterize PAH. In support of a relationship between PAH and IR the Rabinovitch lab has generated preliminary data showing that BMP2R, mutations of which form the genetic basis for familial PAH, induces PPAR gamma gene regulation. While being overweight or obese is not the only determinant of IR being obese increases the likelihood of an individual being insulin resistant. The tendency towards insulin resistance is further accentuated by low levels of physical activity. Adult PAH patients are often obese and inactive (prominent features of IR) and many PAH associated conditions such as sleep apnea and the use of stimulants and appetite suppressants may be by-products of a fundamental metabolic disturbance. The average BMI for patients with PAH in the Stanford PAH Database is 30.6 kg/m2 (n=377). The association of IR with cardiovascular disease and endothelial dysfunction, the association of obesity with IR and the high prevalence of obesity in PAH all suggest that IR may contribute to the pathogenesis of PAH.

Objectives

(1) To review fasting lipid profiles on a convenience cohort of PAH patients and determine the prevalence of insulin resistance

(2) To explore the relationship between IR and clinical status

Methods

We reviewed the clinical characteristics and lipoprotein values on a convenience cohort of 79 patients with PAH from the Stanford PH Database, excluding patients with a known history of liver disease, congenital heart disease (uncorrected) cancer, and diabetes. Patients in the Stanford PH database are followed prospectively while alive and outcomes such as death or transplantation are tracked. The retention rate in this cohort is greater than 90%. The current database includes information on 377 patients, 278 of whom are alive and followed quarterly at Stanford. Detailed information is gathered at the initial visit and each follow-up clinic visit and entered into a relational database. The information includes patient demographics, PH classification, concomitant illnesses, medical and surgical history, family history, medication exposure, NYHA class, exercise capacity (six minute walk test), BMI and diagnostic test results (including pulmonary function tests, echocardiograms, right heart catheterizations, V/Q scans, polysomnograms and chest computed tomography). Statistical analyses consisted of a t test and 1-Way ANOVA for comparisons. Results were considered significant if the p value was < 0.5.

Results

The average BMI of all patients was 29.6 ± 8.4 kg/m2 and 56 patients (71%) were overweight or obese by conventional criteria. The average TG/HDL-C ratio among all 79 patients was 3.1 ± 1.8 with (range 0.8-10.2), consistent with an increased prevalence of insulin resistance. The average TG/HDL ratio in the patients who were overweight or obese was 3.3 ± 2, well above the threshold indicating insulin resistance. In terms of the etiology of PAH among this cohort 20 (25.3%) had iPAH, 18 (22.8%) had PAH associated with anorexigen or stimulant exposure, 16 (20.3%) had PAH associated with collagen vascular disease, 11 (13.9%) had PAH associated with congenital heart disease (CHD); the rest included patients with portopulmonary HTN (3.8%), chronic thrombembolic disease (6.3%), OSA (3.8%), and miscellaneous causes (3.8%) which included 1 patient with sarcoidosis and 2 patients with HIV (TABLE 1.) Thirty-four of the 79 patients (43%) had TG/HDL ratios greater than 3 and were thus presumed to be insulin resistant (IR), while 29/79 or 41.3% had ratios of less than 2 and were insulin sensitive (IS). (TABLE 2) A comparison of patients who insulin sensitive (IS) with a TG-HDL ratio < 2 with those who were insulin resistant (TG-HDL ratio >3) suggests that the two groups were similar with respect to average age, male:female ratio and average BMI. This latter point emphasizes that while BMI influences IR it is not necessarily correlated with it. (FIGURE 1). In comparing the IS and IR groups there were more patients with CHD in the IR group (5 or 14.7%) than in the IS group (1 or 3.4%). In terms of NYHA classification there were significantly more NYHA III/IV patients in the IR group (56%) than in the IS group (48%); similarly there were more NYHA I/II patients in the IS versus the IR group. Hemodynamics were not significantly different among the IR versus IS groups . However, more IR patients required prostanoid therapy (50%) when compared to patients who were insulin sensitive (34.%).

Table 1

	Total (n=79)
Age - (yrs)	45.8±12.2
Gender – No (%)	
Male	19 (24.1)
Female	60 (75.9)
BMI (kg/m^2)	29.6±8.4
Etiology – No (%)	
iPAH	20 (25.3)
Stim & Appetite Supp	18 (22.8)
CHD	11 (13.9)
CVD	16 (20.3)
CTEPH	5 (6.3)
PPHTN	3 (3.8)
OSA	3 (3.8)
Misc	3 (3.8)
6MWT (meters)	386±145
NYHA – No (%)	
I	3 (3.8)
II	31 (39.2)
III	29 (36.7)
IV	11 (13.9)
Unknown	5 (6.9)
Therapies – No (%)	
Prostanoid	20 (25.3)
ETA	11 (13.9)
PDE-I	1 (1.3)
Prostanoid + ETA	10 (12.7)
Prostanoid + PDE-I	3 (3.8)
ETA + PDE-I	3 (3.8)
All	1 (1.3)
None	30 (37.9)
Hemodynamics:	
mPAP – mmHg	55.9±15.3
Cardiac Index – L/min/m^2	2.2±0.7
PVR – WU	12.8±6.5

Table 1 – Total population Demographics.

Table 2

	Insulin Sensitive (n=29)	Insulin Resistant (n=34)
Age - (yrs)	48.17±13.5	43.41±9.6
Gender – No (%)		
Male	6 (20.7)	7 (20.6)
Female	23 (79.3)	27 (79.4)
BMI (kg/m^2)	30.1±9.1	30.1±8.4
Etiology – No (%)		
iPAH	8 (27.6)	10 (29.4)
Stim & Appetite Supp	6 (20.7)	8 (23.6)
CHD	1 (3.4)	5 (14.7)
CVD	8 (27.6)	6 (17.7)
CTEPH	2 (6.9)	1 (2.9)
PPHTN	3 (10.4)	0
OSA	1 (3.4)	1 (2.9)
Misc	0	3 (8.8)
6MWT (meters)	410±163	369±135
NYHA – No (%)		
I	1 (3.9)	1 (2.9)
II	12 (41.4)	11 (32.4)
III	10 (34.5)	13 (38.2)
IV	4 (13.8)	6 (17.7)
Unknown	2 (6.9)	3 (8.8)
Therapies – No (%)		
Prostanoid	5 (17.3)	12 (35.3)
ETA	4 (13.8)	5 (14.7)
PDE-I	1 (3.4)	0
Prostanoid + ETA	5 (17.2)	2 (5.9)
Prostanoid + PDE-I	0	3 (8.8)
ETA + PDE-I	2 (6.9)	1 (2.9)
All	0	0
None	12 (41.4)	11 (32.4)
Hemodynamics:		
mPAP – mmHg	53.1±19.4	57.2±12.6
Cardiac Index – L/min/m^2	2.3±0.5	2.1±0.89
PVR – WU	12.0±6.5	12.9±7

Table 2 – Characteristics based on insulin resistance profile as determined by TG/HDL ratio. TG/HDL ratio <2.0 is considered insulin sensitive, and >3.0 as insulin resistant state.

Legend: iPAH = idiopathic Pulmonary Arterial Hypertension. PAH associated with congential heart diseases (CHD), collagen vasular diseases (CVD), stimulants and appetite suppressants (Stim & Appetite Supp), chronic thromboembolic disease (CTEPH), portopulmonary hypertension (PPHTN), & sleep apnea (OSA). Miscellaneous (Misc) causes include sarcoidosis and HIV. Therapies included prostanoids, endothelin antagonists (ETA), sildenafil (PDE-I), and combination. Hemodynamic measures include mean pulmonary artery pressures (mPAP), cardiac index, and pulmonary vascular resistance (PVR).

Fig 1

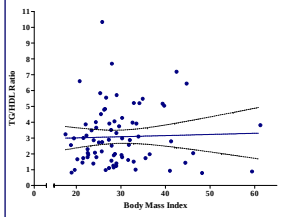

Figure 1 – Insulin resistance profile by TG/HDL is not significantly correlated with body mass index (r2 = 0.001). Solid line represents linear regression line with dotted lines indicating 95% confidence interval. TG/HDL = Triglyceride to High-Density Lipoprotein ratio.

Fig 2

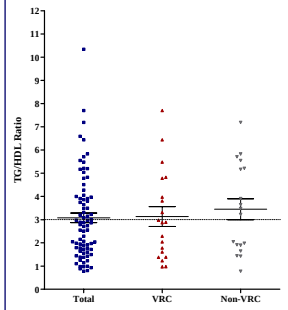

Figure 2 –TG/HDL ratios in vasoreactive (VRC) and non-vasoreactive (Non-VRC) patients. Vasoreactivity was defined as 15% increase in cardiac output and/or 15% drop in pulmonary vascular resistance. Total n=79, VRC n=20, Non-VRC n=18. Dotted line represents TG/HDL ratio 3.0 identifying insulin resistant patients. Bars indicate Mean±SEM.

Discussion & Conclusions

Even with the best current medical management no treatment for PAH has been shown to be universally effective or curative. Lung or heart-lung transplantation is the ultimate therapy for patients with PAH but the 5-year survival after transplantation is only 50%. Clearly newer therapeutic approaches that might slow or halt the progression of PAH are urgently needed. Insulin resistance has clearly been implicated in inflammation, endothelial dysfunction and vascular disease and is strongly associated with adverse clinical outcomes. We have shown that insulin resistance is quite prevalent among PAH patients, and may correlate with severity of disease as illustrated by the significantly higher number of NYHA III/IV patients and those on prostacylin in the IR group compared with the IS group. Among patients who had RHC data there was a non-significnat trend toward less vasoreactivity in those who were IR While the etiology of PAH is likely to be multi-factorial, with genetic and environmental factors contributing, we have shown that insulin resistance may represent an important contributing factor to disease development or disease progression, or both. If this is true then treatment aimed at improving insulin resistance may have benefit for a large percentage of PAH patients. Since both excess adiposity and sedentary behavior adversely affect insulin action weight loss and increased physical activity may represent simple maneuvers that could impact the course of PAH in individual patients. This is the first study to suggest a potential role for insulin resistance in PAH. The data presented is supportive of our hypotheses that (1) IR is a relatively common finding in patients with PAH, and (2) it may contribute to, or be a reflection of, the severity of disease. While these findings are provocative this retrospective study must be interpreted with caution. Further prospective studies with more rigorous study of insulin and lipid metabolism in patients with PAH are underway to better delineate the relationship between IR and PAH.

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