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Metabolic Status in Patients with Operable vs. Inoperable Left-to-Right Shunts

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Data Collection B
Statistical Analysis C
Data Interpretation D
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Background: Previous studies have shown the prognostic value of insulin resistance, hyperuricemia, and dyslipidemia in clinical outcome of pulmonary arterial hypertension. Whether these metabolic derangements are different between operable and inoperable left-to-right shunts is unknown.


Material/Methods: Our study included 116 patients with left-to-right shunts (76 with atrial septal defect and 40 with ventricular septal defect) with or without pulmonary arterial hypertension. Operability of defect closure were assessed by cardiac catheterization and patients were subdivided into an operable group or an inoperable group. The metabolic status, including prediabetes, hyperuricemia, dyslipidemia, hypertension and obesity, were compared between groups.

Results: Patients receiving defect correction had a lower HbA1c (B: 5.52 ± 0.49 vs. 5.71 ± 0.41 , $p=0.042$) and uric acid (C: 358 ± 105 vs. 406 ± 126 , $p=0.029$) but a higher HDLC (D: 1.21 ± 0.33 vs. 1.08 ± 0.22 , $p=0.017$) and BMI (A: 20.4 ± 3.9 vs. 18.8 ± 3.1 , $p=0.023$). Patients in the inoperable group had a higher prevalence of prediabetes (58% vs. 41%, $p=0.076$), hyperuricemia (37.2% vs. 21.9%, $p=0.106$), dyslipidemia (74% vs. 56%, $p=0.049$) but a lower prevalence of hypertension (13.9% vs. 30.1%, $p=0.049$) and obesity (4.6% vs. 12.3%, $p=0.301$). According to logistic regression, only HbA1c (1.76 (0.53, 2.99), HR (95% CI), $p=0.005$) remained significant for pulmonary vascular resistance.

Conclusions: Although prediabetes, hyperuricemia, and dyslipidemia were all more prevalent in patients with inoperable left-to-right shunts, only prediabetes was found to be significantly associated with higher pulmonary vascular resistance.

MeSH Keywords: **Adult • Heart Defects, Congenital • Hypertension, Pulmonary • Insulin Resistance**

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Background

While much is known about metabolic syndrome and systemic vascular disease, the role of metabolic derangements on the pulmonary circulation is poorly studied [1]. Although early closure of the cardiac shunts can obtain a favorable clinical outcome, some defects may be undetected until adulthood and are diagnosed late, when pulmonary vascular lesions have already developed [2]. When the pulmonary vascular resistance (PVR) exceeds 5 Woods, it falls into an inoperable disease state [3,4] and finally progresses to right heart failure. Therefore, slowing or even reversing the disease course is the key to improve survival.

As reported in previous studies, a variety of metabolic derangements, such as insulin resistance, hyperuricemia, and dyslipidemia, are closely related to pulmonary arterial hypertension (PAH) [5–12]. These environmental modifiers may potentiate the effect of persistent left-to-right shunting on the pulmonary vasculature, thereby triggering or worsening PAH [13].

Therefore, we performed this study to characterize the metabolic status of patients with operable vs. inoperable left-to-right shunts and to determine whether these derangements are associated with a more severe disease state that hindered defect closure.

Material and Methods

Study population

Adult patients diagnosed with atrial septal defect (ASD) or ventricular septal defect (VSD) were retrospectively screened at Guangdong Provincial Cardiovascular Institute from 2013 to 2015. We excluded patients with presence of extra-cardiac anomalies, co-morbidity conditions of Down Syndrome, overlapping causes of other types of pulmonary hypertension, overt diabetes, and those taking antihyperglycemic agents. Patients who were candidates for defect correction but refused to receive defect closure were also excluded. Operability of defect closure in patients with VSD/ASD and severity of pulmonary arterial hypertension were assessed by cardiac catheterization. Ethics approval was granted by the hospital Research Ethics Committee.

Definition

According to the WHO definition of metabolic syndrome, we defined systolic BP ≥ 130 mmHg or diastolic BP ≥ 85 mmHg as hypertension, plasma TRIG ≥ 150 mg/ml or HDLC < 40 mg/dl in men or < 50 mg/dl in women as dyslipidemia, and BMI > 30 kg/m² as obesity [14]. But for the Asian population, we defined a BMI

> 25 kg/m² as relatively obese. As proposed by the American Diabetes Association, an HbA1c of $\geq 5.7\%$ is associated with diabetes risk and could be regarded as prediabetes [15,16]. Based on the physiochemical definition of hyperuricemia, uric acid > 416 mmol/l is hyperuricemia [17].

According to the 2010 ESC guidelines for the management of adult congenital heart disease, patients with significant shunt (Qp: Qs > 1.5 or with signs of RV volume overload) and PVR < 5 WU should undergo defect closure. Surgeries or percutaneous interventions are contraindicated for patients with PVR > 5 WU and a net left-to-right shunting (Qp/Qs) less than 1.5 [3]. Patients were divided into operable and inoperable groups based on these criteria.

Data collection

Fasting venous blood samples were drawn to measure lipid profile (total cholesterol, low-density lipoprotein, triglycerides, and high-density lipoprotein), glycosylated hemoglobin A1c (HbA1c), uric acid (UA), and NT-proBNP. From the diagnostic right heart catheterization, heart rate (HR), systemic systolic and diastolic blood pressures (shtn and dhtn), right atrial pressure (RAP), pulmonary artery pressures (PAP), pulmonary artery wedge pressure (PAWP), cardiac output (CO), and cardiac index (CI) were recorded.

Data analysis

Data was analyzed using SPSS version 20.0 software (SPSS Statistics version 20, IBM Corporation, Armonk, NY, USA). Results are expressed as mean \pm standard deviation for continuous variables or as number of patients and percentages for categorical variables. Key clinical and hemodynamic parameters for operable and inoperable patients were compared using the independent-samples *t* test. Comparisons of the prevalence of prediabetes, hyperuricemia, and dyslipidemia were evaluated by the chi-square or Fisher exact test. Age, sex, uric acid, BMI, and lipid profile were used to evaluate the relationship with pulmonary vascular resistance by univariate and multivariate logistic regression model. All p-values were 2-sided, and a value at $p < 0.05$ was considered statistically significant.

Results

Our center evaluated a total of 116 eligible patients with a mean age of 39 ± 13 years (83 females and 33 males, ASD=76, VSD=40). Patients were divided into operable (n=73) and inoperable groups (n=43) according to 2010 ESC guidelines for the management of adult congenital heart disease [3]. Demographics, laboratory blood test results, and hemodynamic details are shown in Table 1.

Table 1. Comparisons of patients' demographics, laboratory blood tests and hemodynamic details.

	Operable (n=73)	Inoperable (n=43)	p Value
AGE (years)	42±14	33±11	<0.0001
BMI (kg/m ²)	20.4±3.9	18.8±3.1	0.023
HbA1c (%)	5.52±0.49	5.71±0.41	0.042
NTproBNP (pg/ml)	779.2±1317	787±1398	0.974
CREA (umol/l)	66.8±17.3	64.9±18.9	0.601
UA (mmol/l)	358±105	406±126	0.029
HGB (g/l)	135±14	150±33	0.001
CHOL (mmol/l)	4.31±0.8	4.08±0.71	0.126
TRIG (mmol/l)	1.05±0.52	1.01±0.33	0.644
HDLC (mmol/l)	1.21±0.33	1.08±0.22	0.017
LDLC (mmol/l)	2.52±0.71	2.44±0.64	0.054
HR (bpm)	81±11	83±12	0.522
RA (mmHg)	6.5±3.4	6.5±3.3	0.99
MPAP (mmHg)	36.8±18	70.6±13.4	<0.0001
PAWP (mmHg)	10±3	10.5±2.8	0.372
OXYGEN (%)	70.3±8.3	66.9±6.6	0.024
QP/QS	2.3±0.9	0.97±0.29	<0.0001
CI (L/min)	3.52±0.96	3.7±0.95	0.234
PVR (woods)	3.79±2.9	15.5±6.7	<0.0001
SVR (woods)	18.3±6.6	16.5±4.8	0.127
PVR/SVR	0.21±0.13	0.96±0.38	<0.0001

BMI – body mass index; CREA – creatinine; UA – uric acid; HGB – hemoglobin; CHOL – cholesterol; TRIG – triglyceride; HDLC – high density lipoprotein cholesterol; LDLC – low density lipoprotein cholesterol; HR – heart rate; RA – right atrial pressure; MPAP – mean pulmonary arterial pressure; PAWP – pulmonary artery wedge pressure; OXYGEN – mixed venous oxygen saturation; QP/QS – the ratio of pulmonary circulation and systemic circulation; CI – cardiac index; PVR – pulmonary vascular resistance; SVR – systemic vascular resistance; PVR/SVR – the ratio of pulmonary vascular resistance and systemic vascular resistance. Data are presented as means ±SD.

As shown in Table 1, age, BMI, HbA1c, uric acid, and HDLC were significantly different between operable and inoperable groups ($p < 0.05$). Patients receiving defect correction were relative older (42 ± 14 vs. 33 ± 11 , $p < 0.0001$) and had a lower HbA1c (5.52 ± 0.49 vs. 5.71 ± 0.41 , $p = 0.042$) and uric acid (358 ± 105 vs. 406 ± 126 , $p = 0.029$) but a higher HDLC (1.21 ± 0.33 vs. 1.08 ± 0.22 , $p = 0.017$) and BMI (20.4 ± 3.9 vs. 18.8 ± 3.1 , $p = 0.023$) (Figure 1).

According to the above-defined metabolic disturbances, patients in the inoperable group had a higher prevalence of pre-diabetes (58% vs. 41%, $p = 0.076$), hyperuricemia (37.2% vs. 21.9%, $p = 0.106$), and dyslipidemia (74% vs. 56%, $p = 0.049$), but a lower prevalence of hypertension (13.9% vs. 30.1%, $p = 0.049$) and obesity (4.6% vs. 12.3%, $p = 0.301$) (Figure 2).

On univariate logistic regression analysis, age, BMI, HbA1c, uric acid, HDLC, and blood pressure (BP) were found to be associated with pulmonary vascular resistance. However, when all these factors were entered into the multivariate logistic regression model, only age and HbA1c remained significant (Table 2).

Discussion

Metabolic syndrome is a known risk factor for coronary artery disease. However, whether a similar effect occurs in pulmonary circulation remains unclear [1]. Previous studies have shown the prognostic value of insulin resistance, hyperuricemia, and dyslipidemia in the clinical outcome of PAH [5–12].

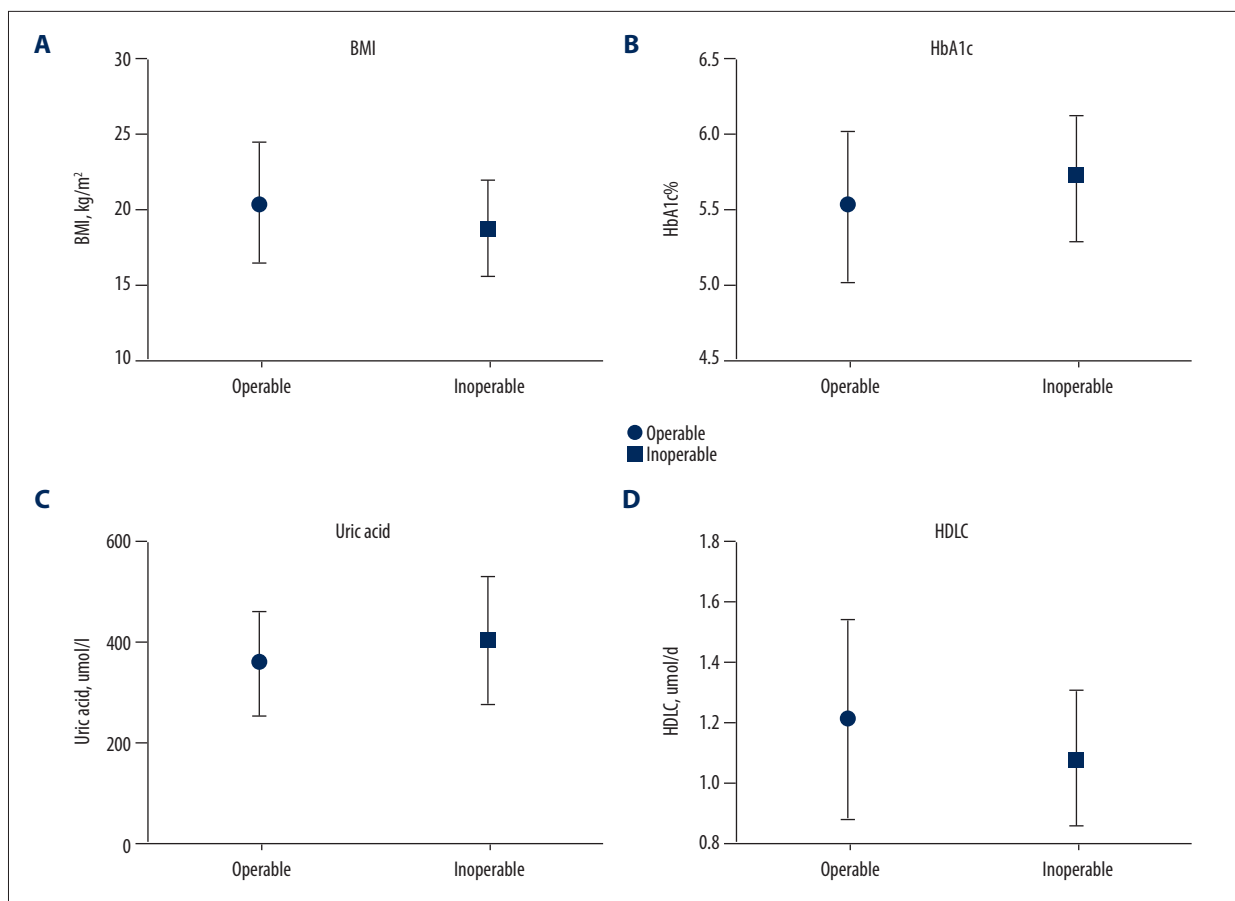


Figure 1. Comparisons of metabolic status in patients with operable vs. inoperable left-to-right shunts. Patients receiving defect correction had a lower HbA1c (**B**: 5.52 ± 0.49 vs. 5.71 ± 0.41 , $p=0.042$) and uric acid (**C**: 358 ± 105 vs. 406 ± 126 , $p=0.029$) but a higher HDLC (**D**: 1.21 ± 0.33 vs. 1.08 ± 0.22 , $p=0.017$) and BMI (**A**: 20.4 ± 3.9 vs. 18.8 ± 3.1 , $p=0.023$).

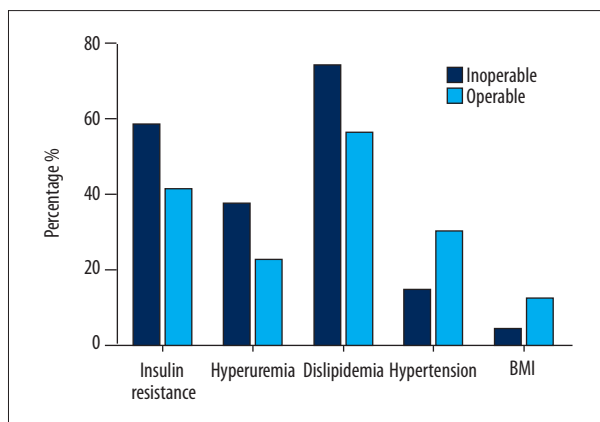


Figure 2. Prevalence of insulin resistance, hyperuricemia, dyslipidemia, and obesity in operable and inoperable groups. According to the above-defined metabolic disturbances, patients in the inoperable group had a higher prevalence of prediabetes/insulin resistance (58% vs. 41%, $p=0.076$), hyperuricemia (37.2% vs. 21.9%, $p=0.106$), and dyslipidemia (74% vs. 56%, $p=0.049$) but lower prevalence of hypertension (13.9% vs. 30.1%, $p=0.049$) and obesity (4.6% vs. 12.3%, $p=0.301$).

This suggests that these abnormal metabolic statuses play significant pathophysiologic roles in disease progression.

As shown in our study, prediabetes, low HDLC, and hyperuricemia were more prevalent in inoperable patients. They had a higher HbA1c and uric acid, but a lower HDLC. Results of univariate logistic regression also showed the relationship between pulmonary vascular resistance and the above-mentioned metabolic factors. However, although several reported studies have documented the relationship between hyperuricemia, low HDLC, and PAH [8–12], we only found HbA1c to be a significant risk factor for higher PVR, as shown in the multivariate logistic regression model. It is possible that hyperuricemia and low HDLC were simply 2 confounding factors associated with insulin resistance.

However, it is unclear whether insulin resistance is the cause or just a result of pulmonary arterial hypertension. Bone morphogenic protein receptor type 2 (BMPR2) is a well-known gene related to pulmonary arterial hypertension. West et al. studied the relationship between BMPR2 and pulmonary hypertension, and found that activation of BMPR2 mutation was associated

Table 2. Univariate and multivariate logistic regression between potential risk factors and PVR.

Variable	HR (95%CI)	P value	HR (95%CI)	P value
Age	-0.056 (-0.089, -0.023)	0.001	-0.08 (-0.12, -0.036)	<0.0001
Gender	0.417 (-0.44, 1.25)	0.343	-	-
BMI	-0.13 (-0.24, -0.015)	0.026	-0.13 (-0.26, -0.0005)	0.051
HbA1c	0.87 (0.02, 1.7)	0.045	1.76 (0.53, 2.99)	0.005
UA	0.004 (0.0003, 0.0007)	0.035	0.003 (0.0013, 0.0073)	0.165
HDLC	-1.53 (-2.93, -0.12)	0.034	-1.1 (-2.74, 0.54)	0.187
CHOL	-0.40 (-0.91, 0.11)	0.128	-	-
TRIG	-0.19 (-1.04, 0.64)	0.641	-	-
LDLC	-0.17 (-0.72, 0.38)	0.343	-	-
shtn	-0.03 (-0.06, -0.005)	0.019	-0.03 (-0.07, -0.016)	0.202
dhtn	-0.03 (-0.06, -0.008)	0.121	-	-

PVR – pulmonary vascular resistance; BMI – body mass index; UA – uric acid; CHOL – cholesterol; TRIG – triglyceride; HDLC – high density lipoprotein cholesterol; LDLC – low density lipoprotein cholesterol; shtn – systolic blood pressure; dhtn – diastolic blood pressure.

with early insulin resistance [18]. It is also possible that other undiscovered genes could predispose patients to early onset of insulin resistance and subsequent pulmonary arterial hypertension. However, insulin resistance could also be considered a result of long-term hypoxic damage of pancreatic beta cells, and Daniele et al. reported that the decreased blood flux and hypoxia caused by atherosclerosis could cause damage to beta cells [19]. Similarly, hypoxia caused by severe PAH or the presence of right-to-left shunt could also lead to dysfunction of beta cells and subsequent prediabetic or diabetic conditions, which may subsequently aggravate PAH.

Although the hypotheses mentioned above have not yet been confirmed, it is clear that the prediabetic condition will further damage the pulmonary vascular system and contribute to disease progression. High glucose concentrations induce mitogen-activated protein kinase/phosphatidylinositol 3-kinase(PI3K)-dependent upregulation of PDGF receptor-beta and potentiate migration and proliferation of smooth muscle cells (SMC) [20,21]. The inflammatory milieu associated with IR, as demonstrated by high levels of pro-inflammatory biomarkers such as C-reactive protein, interleukin-6, and myeloperoxidase, is thought to underlie the associated endothelial dysfunction and vascular disease [22]. These are all key factors associated with vascular remodeling, which results in higher pulmonary vascular resistance.

Thus, no matter which is the cause, it is crucial to stop this vicious cycle, hoping to slow disease progression or even reverse it. For patients with persistent left-to-right shunting, insulin resistance or prediabetes could probably serve as a second insult

that accelerates the onset or progression of pulmonary vascular disease and pulmonary arterial hypertension [22]. Thus, it is possible that correcting this derangement would improve hemodynamic or pulmonary vascular disease in patients with congenital heart diseases. Several investigators have demonstrated that antidiabetic drugs like pioglitazone and metformin might reverse SMC proliferation and vascular remodeling in PAH patients [13,23–25]. With the concept of “treat and close” for those previously inoperable cardiac shunts, modifying the metabolic dysfunction in combination with pulmonary vasodilators is an exciting prospect for the treatment of this devastating illness and would make conditions more favorable for repair.

Limitations

Although there are several hypotheses that could explain this phenomenon, a cause-effect relationship cannot be confirmed due to the cross-sectional nature of this study. In addition, we used HbA1c as an indicator of insulin resistance, and this estimation may not be accurate. Also, the relatively small number of patients without follow-up data may be another limitation. Mechanistic studies to determine the effect of metabolic disturbances on pulmonary circulation and randomized controlled studies to detect the therapeutic effect of antidiabetic drugs on CHD-PAH are warranted.

Conclusions

In conclusion, although prediabetes, hyperuricemia, and dyslipidemia were all more prevalent in patients with inoperable

left-to-right shunts, only prediabetes was found to be significantly related to higher pulmonary vascular resistance. However, whether improving insulin resistance prevents or reverses vascular remodeling, thereby allowing inoperable patients to receive surgery, is in need of further investigation.

References:

1. Assad TR: Metabolic dysfunction in pulmonary arterial hypertension. *Curr Hypertens Rep*, 2015; 17(3): 20
2. Duffels MG, Engelfriet PM, Berger RM et al: Pulmonary arterial hypertension in congenital heart disease: an epidemiologic perspective from a Dutch registry. *Int J Cardiol*, 2007; 120: 198–204
3. Baumgartner H, Bonhoeffer P, De Groot NM et al: ESC Guidelines for the management of grown-up congenital heart disease (new version 2010). *Eur Heart J*, 2010; 31: 2915–57
4. Warnes CA, Williams RG, Bashore TM et al: ACC/AHA 2008 Guidelines for the Management of Adults with Congenital Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to develop guidelines on the management of adults with congenital heart disease). *Circulation*, 2008; 118(23): e714–833
5. Zamanian RT, Hansmann G, Snook S et al: Insulin resistance in pulmonary arterial hypertension. *Eur Respir J*, 2009; 33: 318–24
6. Naderi N, Boobejame P, Bakhshandeh H et al: Insulin resistance in pulmonary arterial hypertension, is it a novel disease modifier? *Res Cardiovasc Med*, 2014; 3: e19710
7. Pugh ME, Robbins IM, Rice TW et al: Unrecognized glucose intolerance is common in pulmonary arterial hypertension. *J Heart Lung Transplant*, 2011; 30: 904–11
8. Heresi GA, Aytekin M, Newman J et al: Plasma levels of high-density lipoprotein cholesterol and outcomes in pulmonary arterial hypertension. *Am J Respir Crit Care Med*, 2010; 182: 661–68
9. Zhao QH, Peng FH, Wei H et al: Serum high-density lipoprotein cholesterol levels as a prognostic indicator in patients with idiopathic pulmonary arterial hypertension. *Am J Cardiol*, 2012; 110: 433–39
10. Nagaya N, Uematsu M, Satoh T et al: Serum uric acid levels correlate with the severity and the mortality of primary pulmonary hypertension. *Am J Respir Crit Care Med*, 1999; 160(2): 487–92
11. Voelkel MA, Wynne KM, Badesch DB et al: Hyperuricemia in severe pulmonary hypertension. *Chest*, 2000; 117(1): 19–24
12. Bendayan D, Shitrit D, Ygla M et al: Hyperuricemia as a prognostic factor in pulmonary arterial hypertension. *Respir Med*, 2003; 97(2): 130–33
13. Hansmann G, Wagner RA, Schellong S et al: Pulmonary arterial hypertension is linked to insulin resistance and reversed by peroxisome proliferator-activated receptor-gamma activation. *Circulation*, 2007; 115: 1275–84
14. Grundy SM, Brewer HB Jr., Cleeman JI et al: Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation*, 2004; 109: 433–38
15. American Diabetes Association: Standards of medical care in diabetes – 2011. *Diabetes Care*, 2011; 34(Suppl. 1): S11–61
16. Belly MJ, Tiede H, Morty RE et al: HbA1c in pulmonary arterial hypertension: A marker of prognostic relevance? *J Heart Lung Transplant*, 2012; 31: 1109–14
17. Khanna D, Fitzgerald JD, Khanna PP et al: 2012 American College of Rheumatology guidelines for management of gout. Part 1: Systematic non-pharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care Res (Hoboken)*, 2012; 64: 1431–46
18. West J, Niswender KD, Johnson JA et al: A potential role for insulin resistance in experimental pulmonary hypertension. *Eur Respir J*, 2013; 41(4): 861–71
19. Rosso D, Carnazzo G, Giarelli L et al: Atherosclerosis and pancreatic damage. *Arch Gerontol Geriatr*, 2001; 32: 95–100
20. Campbell M, Allen WE, Silversides JA, Trimble ER: Glucose-induced phosphatidylinositol 3-kinase and mitogen-activated protein kinase-dependent upregulation of the platelet-derived growth factor-beta receptor potentiates vascular smooth muscle cell chemotaxis. *Diabetes*, 2003; 52: 519–26
21. Grinnan D, Farr G, Fox A: The role of hyperglycemia and insulin resistance in the development and progression of pulmonary arterial hypertension. *J Diabetes Res*, 2016; 2016: 2481659
22. Moral-Sanz J, Moreno L, Cogolludo A: Pulmonary vascular function in insulin resistance and diabetes. *Curr Vasc Pharmacol*, 2014; 12: 473–82
23. Hansmann G, de Jesus Perez VA, Alastalo TP et al: An antiproliferative BMP-2/PPARgamma/apoE axis in human and murine SMCs and its role in pulmonary hypertension. *J Clin Invest*, 2008; 118: 1846–57
24. Rabinovitch M: PPARgamma and the pathobiology of pulmonary arterial hypertension. *Adv Exp Med Biol*, 2010; 661: 447–58
25. Li S, Han D, Zhang Y et al: Activation of AMPK prevents monocrotaline-induced extracellular matrix remodeling of pulmonary artery. *Med Sci Monit Basic Res*, 2016; 22: 27–33

Conflict of interest

None.