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A BRIEF SUMMARY OF THE RESULTS OF THE 6TH WORLD SYMPOSIUM ON PULMONARY HYPERTENSION IN NICE IN 2018: VIEW OF A YOUNG SCIENTIST

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The 1st World Symposium on the Problem of Pulmonary Hypertension (PH) was held in Geneva in 1973 and following the publication of the Evian Classification of PH in 1998 after the Second World Symposium, was traditionally held every 5 years (Venice 2003, Dana Point 2008, Nice 2013).

In 2018, the venue of the symposium was Nice with amazing sea views and March snowfall.

The main objective of this symposium was to review the main scientific achievements in the field of PH in the past 5 years and discuss the possibility of conducting joint research programs to replenish the evidence base.

At the beginning of the symposium, attention was paid to the pathophysiology of PH. According to the Guignabert's report the contribution of inflammation in the process of remodeling of the pulmonary vascular bed, the possibility of identification the proinflammatory phenotype of the pulmonary arteries (PA) endothelial cells were discussed.

The creating of biobank and developing a new genetic panel for PAH patients are the perspective in the field of genetics.

In the report of Morrel N.W. the new genetic mutations in PAH with a high level of evidence such as P-type ATPase (ATP13A3), growth and differentiation factor 9 (GDF2) (BMP9), SRY (Sex determining region Y) Box 17 (SOX17) and Aquaporin 1 (AQP1) with a lower level of evidence were presented.

Pullamsetti S.S. was demonstrated the novel channelopathies in PAH – calcium activated chloride (TMEM16A) channels, that have been identified in many epithelial and endothelial cells as well as in smooth muscle cells. Upregulated chloride channels cause depolarization in IPAH and increased PA contraction and remodeling that is important in disease pathogenesis. It indicates the discovery of new mechanisms that induce the IPAH and the possibility of creating specific drug therapies that effect on this pathway.

Better understanding the bidirectional regulatory mechanisms between metabolic remodeling and the epigenome in PH are also the future directions.

It is known that bone morphogenetic protein receptor type 2 (BMPR2) is frequently downregulated in IPAH and some PAH associated forms. Intervention targeting BMPR2 in IPAH and PAH patients are under development.

It has been supposed, that phenotyping of PH patients for further determination of treatment strategy and prognosis is necessary.

PAH phenotype has changed: patients become older at the time of diagnosis verification, with higher body mass index and multiple comorbidities.

With cytokine proteomics the new PAH phenotypes which presented as 4 immune clusters were established, that was demonstrated in report of Rabinovitch M.

The one of the future direction is to assess the impact of genetic mutations on clinical phenotypes and outcomes in patients with PH.

For the first time in the past 20 years the issue of changing the diagnostic criteria in PH was discussed. It has been supposed to reduce the threshold of mean PA pressure (mPAP) to 20 mm Hg according to right heart catheterization data (RHC). However, these changes may be applicable only in PH Group 1 and 3. Whereas the previous threshold >25 mm Hg was proposed to leave in patients with chronic thromboembolic PH (CTEPH).

It has been supposed to reduce the threshold of mPAP to 20 mm Hg in PH Group 2 patients also. However, it was suggested to exclude the value of the diastolic pressure gradient in evaluation the isolated or mixed post- and precapillary PH.

The modified criteria for an isolated post-capillary PH are: the PA wedge pressure (PAWP) >15 mm Hg, mPAP >20 mm Hg and the pulmonary vascular resistance (PVR) <3 Wood Units. While the criteria for mixed post- and precapillary PH are: PAWP >15 mm Hg, mPAP >20 mm Hg and PVR >3 Wood Units.

In patients with PAWP between 13-15 mm Hg and high/intermediate probability of PH and heart failure (HF) with preserved ejection fraction (EF), a fluid loading challenge should be considered with 500 ml of saline over 5 minutes during RHC. A PAWP >18 mm Hg immediately after fluid administration is considered abnormal.

At the same time, the initiation of various specific drugs in patients with PH and HF with a preserved EF was unsuccessful and even unsafe according to the randomized clinical trials results.

The assessment of right ventricular (RV) two-dimensional (2D) strain by Echo or cardiac magnetic resonance imaging (MRI) were demonstrated as the method, that estimates subclinical RV impairment before the development of the more conventional abnormalities of RV performance. RV free wall longitudinal strain is an index of RV myocardial function and is a powerful predictor of outcome.

The photos show some Russian delegators from Moscow, who participated in 6th World Symposium on PH 2018.

From left to right:: *Taran Irina Nikolaevna – postgraduate student of Department of Pulmonary Hypertension and Heart Diseases, National Medical Research Center of cardiology Ministry of Healthcare of Russian Federation;*

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Nakonechnikov Sergej Nikolaevich – Dr. Med. Sci., Prof., Deputy director general for Telemedicine Technologies and Public Communications, National Medical Research Center of cardiology Ministry of Healthcare of Russian Federation;

Gorbachevskij Sergej Valer'evich – Dr. Med. Sci., Prof., cardiovascular surgeon, head of department of Surgical Heart Diseases with Progressive Pulmonary Hypertension, National Medical Research Center of Cardiovascular surgery of Bakulev A.N. Ministry of Healthcare of Russian Federation;

Volkov Aleksandr Vital'evich – PhD., head of department of functional and ultrasound methods, Federal State Budget Research Organization Scientific Institute of Rheumatology of VA. Nasonovoj.

The conduction of multicenter prospective clinical trials with inclusion of different groups of patients with PH to determine the role of the Echo and MRI in assessment of the RV strain in clinical practice is required.

The attention was also focused on the evaluation of the RV – PA coupling.

There are several approaches for evaluation of RV – PA coupling.

The first method is the Pressure-Volume loops analysis. It consists of invasive assessment of the pressure and volume of the ventricles, which is reflected in the diagrams and is subsequently used to calculate cardiovascular coupling.

The RV–PA coupling is calculated as Ea:Emax ratio, where Ea is the effective arterial elastance and Emax is the ventricular end-systolic elastance. Effective arterial elastance was calculated as follows: Ea = (mPAP – PAWP)/SV, where SV is the stroke volume and ventricular end-systolic elastance was calculated by the formula: Emax = mPAP/ESV, where ESV is the RV end-systolic volume.

The second technique for assessing RV – PA coupling is the use of 2D and three-dimensional (3D) transthoracic Echo with the evaluation of mPAP, PWAP and SV by 2D Echo and RV ESV by 3D with subsequent calculation of RV – PA coupling according to the formulas.

In the National Medical Research Center of Cardiology in department of pulmonary hypertension and heart diseases and department of ultrasound techniques a scientific work on dynamics of RV – PA coupling in patients with IPAH and inoperable CTEPH with various specific therapies is carried out.

The close associations between RV – PA coupling and parameters from risk stratification scale were revealed, that reflected the usefulness of RV – PA coupling in assessment of severity in PH patients. Furthermore, it is interesting to use this method in phenotyping of IPAH and CTEPH patients. The results of the study were presented on the symposium during the poster session (Picture 1).

The evaluation of the ratio between tricuspid annular plane systolic excursion (TAPSE) and systolic PAP (SPAP) was the third method of RV – PA coupling determination as was demonstrated in Noodredegraaf's report. However, the TAPSE/SPAP ratio may have prognostic information, but may not represent coupling.

In the section on diagnosis and risk stratification of PH patients, the use of cardiopulmonary exercise testing (CPET) and its role in clinical practice were discussed. CPET data provide information about severity, risk and prognosis of patients with PH. The conduction of CPET in dynamics is necessary in assessing the efficacy of specific therapy and rehabilitation programs.

The experience of department of pulmonary hypertension and heart diseases of National Medical Research Center of cardiology about the value of CPET in assessment of severity in patients with PAH was also presented during the poster session. The study included 55 patients and before CPET performing the majority of patients (53%) had a high risk of mortality during 1 year. After CPET performing we revealed, that an additional 18% of patients, who had been earlier in intermediate risk, had a high risk of mortality during 1 year, that influenced on a decision about more aggressive specific therapy for these patients (Picture 2).

It is possible to make a detailed evaluation of the 3D structure of the pulmonary vascular bed by MRI with subsequent printing of the PA tree in a 3D format. The main advantages of this method are safety and lower cost in comparison with invasive methods. This technique may be helpful in detailed assessment of the level and character of thrombotic lesions of the PA's both for endovascular and cardiovascular surgeons in CTEPH patients' management.

In the field of CTEPH patients the new intra – operative classification was proposed (level of anatomical disease rather than type of clot).

Level 0 (Old type IV)	No evidence of CTEPH in either lung
Level I (Old type I or II)	Disease in the main PA's
Level IC	Complete occlusion of the entire lung
Level II (Old type I or II)	Disease starting at the level of lobal arteries, or in the main descending PA's
Level III (Old type III)	Disease starting in the segmental levels
Level IV (Old type III)	Disease starting at the level of sub-segmental arteries

According to the results of RACE study a new algorithm for management of patients with inoperable CTEPH was proposed. It was indicated that the method of transluminal balloon angioplasty of PA's could be considered in this cohort of patients only with specific drugs treatment.

The strategy of treatment in patients with PAH, groups 2 and 3, did not undergo significant changes. The attention was focused on prospects of initial combination therapy in patients with intermediate and high risk of mortality. The method of therapy optimization by switching from one class of specific drug to another due to intolerability, inadequate response or failure to achieve the treatment goals requires further study.

INFLUENCE OF INITIAL RIOCIGUAT MONOTHERAPY AND TRANSITION FROM SILDENAFIL TO RIOCIGUAT THERAPY IN PATIENTS WITH IDIOPATHIC PULMONARY ARTERIAL HYPERTENSION ON RIGHT HEART REMODELING AND RIGHT VENTRICULAR – PULMONARY ARTERIAL COUPLING

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Objective: To evaluate the influence of riociguat on WHO functional class (FC), parameters of transthoracic Echo in naïve patients (pts) with idiopathic pulmonary arterial hypertension (IPAH) and in those who have failed to achieve treatment goals with sildenafil.

Materials and methods: The study included 22 IPAH pts: 14 - treatment-naïve pts and 8 pts, who failed to achieve treatment goals with sildenafil. The baseline characteristics of subgroups are presented in the Table 1. Riociguat was initiated for all pts at baseline with a gradual dose increase according to the dose titration algorithm. At baseline and after 24 weeks of riociguat treatment all pts were assessed for WHO FC, right heart remodeling parameters, interventricular interaction, and right ventricular – pulmonary arterial coupling (RVPAC) by 2D and 3D Echo. The RVPAC was calculated as Ea/Emax ratio, where Ea is the effective arterial elastance and Emax is the ventricular end-systolic elastance.

Results are demonstrated in Figures 1-6 and Table 2.

Figure 1.
The dynamics of 6MWT after 24 weeks of treatment.

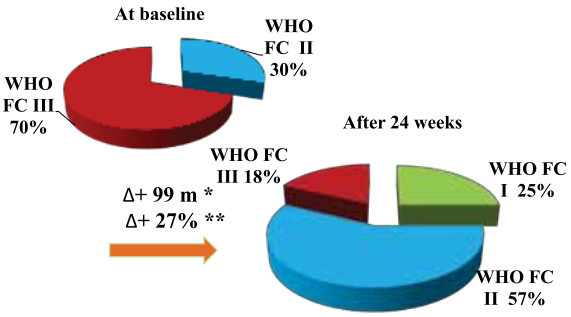


Figure 2,3,4. The dynamics of TAPSE, RV FAC and dIE after 24 weeks of riociguat treatment.

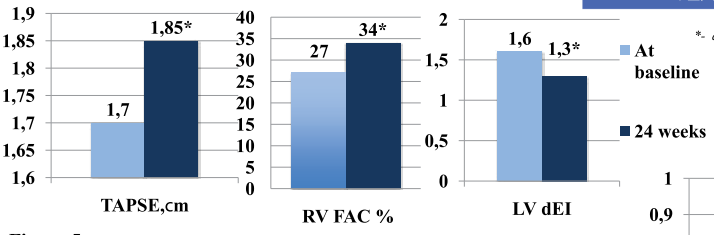


Figure 5 .
The dynamics of RV EF, RV EDV and ESV after 24 weeks of treatment.

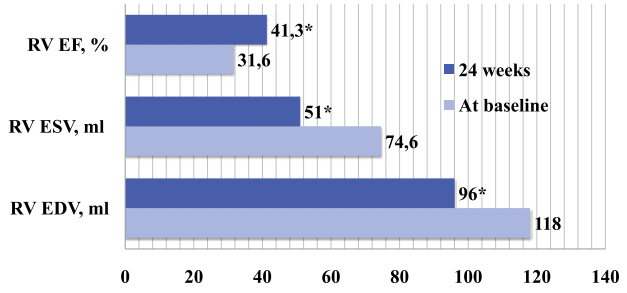


Table 1. Characteristics of IPAH pts subgroups at baseline.

Baseline parameters	Overall IPAH group (n =22)	Treatment- naïve subgroup (n= 14)	Treatment - switch subgroup (n=8)
Age, years	42,5 [34,5; 50]	42 [34,5; 43,5]	42 [33; 50]
Functional status			
FC I/II/III/IV (WHO)	0/7/15/0	0/4/10/0	0/3/5/0
6MWT, m	400 [320;440]	400 [300; 478]	371 [329;439]
VO_2 peak, ml/kg/min	9,9 [8; 14]	9 [7,8;12,95]	11 [8;14]
VE/VCO_2 slope*	38 [32; 49]	42 [36; 55]	33 [30;39,9]
2D and 3D echocardiography			
RA area, cm^2	20 [16; 23,5]	19,2 [16,6; 25]	20 [17,0; 23]
RVBD, cm	4,4 [4; 4,6]	4,45 [4,1; 4,65]	4,5 [3,8; 4,6]
TAPSE, cm	1,7 [1,49; 1,8]	1,5[1,34; 1,7]	1,8 [1,7; 1,9]
LV dEI	1,6 [1,48; 1,8]	1,7 [1,6; 1,8]	1,46 [1,4; 1,57]
RV FAC, %	27 [23; 32]	27,7 [21,5; 32]	26 [24; 29,5]
SPAP, mmHg	78 [75; 105]	78 [75; 110]	78 [65; 95,5]
mean PAP, mmHg	57 [47; 68]	56,5 [47; 73]	57 [43; 63,5]
RV EDV, ml	118 [95,7; 145,6]	120 [108; 142]	116 [94; 140]
RV ESV, ml	74,6 [64,5; 86,2]	77 [67,9; 85,6]	74,6 [62; 102,7]
RV EF, %	31,6 [22; 36]	31 [22; 36]	32 [23; 36,5]
PA Ea, mm Hg/ml*	0,72 [0,56; 1,02]	0,9 [0,7; 1,07]	0,57 [0,39; 0,63]
RV Emax, mm Hg/ml	0,8 [0,63; 0,87]	0, 8[0,53; 0,84]	0,78 [0,67; 1]
RVPAC*	0,9 [0,7; 1,32]	1,1 [0,86;1,48]	0,69 [0,47; 0,86]

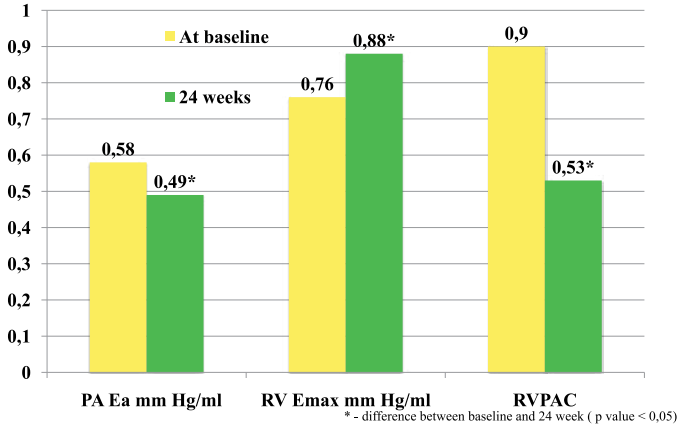
All data are presented as mediana ± IQR; *- p value < 0,05 (lower values for treatment – switch subgroup);FC (WHO)- functional class according to the World Health Organization classification, 6MWT- 6-minute walking test, Vo2 peak- peak oxygen uptake, VE/Vco2 - ventilation equivalents for Co2 , RA- right atrium, RVBD- right ventricular basal diameter, TAPSE- tricuspid annular plane systolic excursion, dEI- diastolic index eccentricity of left ventricular, FAC RV - RV fractional area change, SPAP- systolic pulmonary arterial pressure, RV EDV – end diastolic volume of RV, RV ESV – end systolic volume of RV, RV EF- RV ejection fraction.

Table 2. The dynamics of VO2 peak and VE/Vco2 after 24 weeks of treatment.

Parameters	At baseline	24 week	p*
Vo2 peak, ml/kg/min	8,8 [7,1; 11,9]	11,5[10,2;12]	0,01
VE/Vco2 slope	38,8 [32,8; 48,5]	33,6[29,5;42,7]#	0,02

**- difference between baseline and week 24; # - more significant changes at week 24 in treatment –naïve group.*

Figure 6 .
The dynamics of RVPAC after 24 weeks of riociguat treatment.



* - difference between baseline and 24 week (p value < 0,05)

Conclusion: Riociguat monotherapy and transition from sildenafil to riociguat appeared equally effective on IPAH pts with a pronounced improvement in right heart remodeling and RVPAC.

Picture 1. The influence of riociguat therapy on right heart remodeling and RV –PA coupling.

THE VALUE OF CARDIOPULMONARY EXERCISE TEST IN ASSESMENT OF THE SEVERITY OF PULMONARY ARTERIAL HYPERTENSION PATIENTS

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Objective: To evaluate the impact of cardiopulmonary exercise test (CPET) on fatal events risk stratification in pts with pulmonary arterial hypertension (PAH).

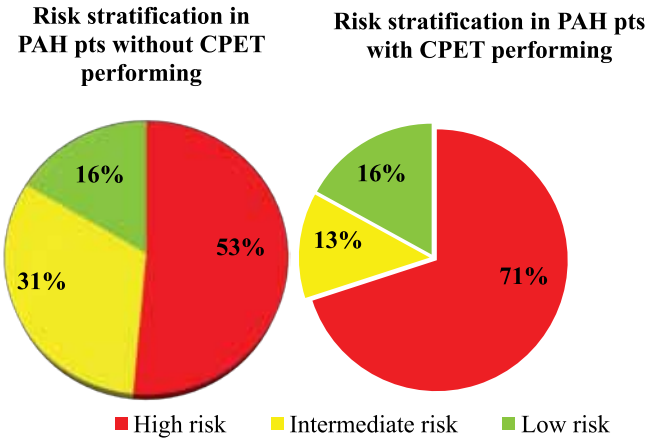
Materials and methods: 55 pts with PAH (mean age 43,4+10,73 years) were underwent CPET on cycle ergometry. Oxygen uptake (VO2), carbon dioxide output (VCO2), minute ventilation (VE) were measured breath-by -breath.

Table 1. Characteristics of the PAH patients.

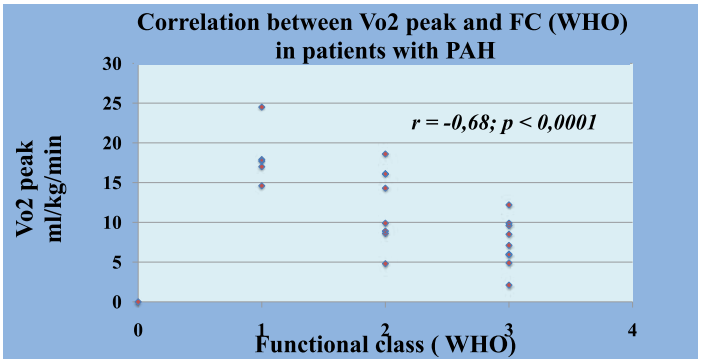
Parameters	IPAH (n=48)	PAH, associated with		
		CHD (n=5)	CTD (n=1)	Drugs and toxins (n=1)
Age, years	43,1± 11	36±1	61	41
Sex (n - female)	42	3	1	1
6MWT, m	411,6±120	485±117,9	320	433
FC (WHO) I/II (n)	9/22	2/1	0/1	1/0
FC (WHO) III/IV (n)	17/0	2/0	0/0	0/0
RA area ,cm2	23,8±7,7	16,5±6	12	32
RVBD, cm	3,7±0,61	3,1±0,98	2,8	5
IVC, cm	2,1±0,29	2,0±0,2	1,8	2,0
Pericardial effusion: Minimal /small (n)	6/2	0/0	0/1	0/0
Vo2 peak, ml/kg/min	10,9±5,1	13,5±5,9	9,6	8,5
VE/Vco2 slope	46±19,7	43,2±8,3	40,9	73
Right heart catheterization				
mPAP , mm Hg	54,2 ±11	48,5 ±17,6	30	46
mRAP, mm Hg	8±5,5	5,6±5	1	1
SVo2 , %	58,6±8,8	78,5±6,3	65	74
CI, l/min/m²	1,96±0,6	2,9	2,1	1,7
PVR dyn*s*sm-5	1270±625	1330±723	594	1025

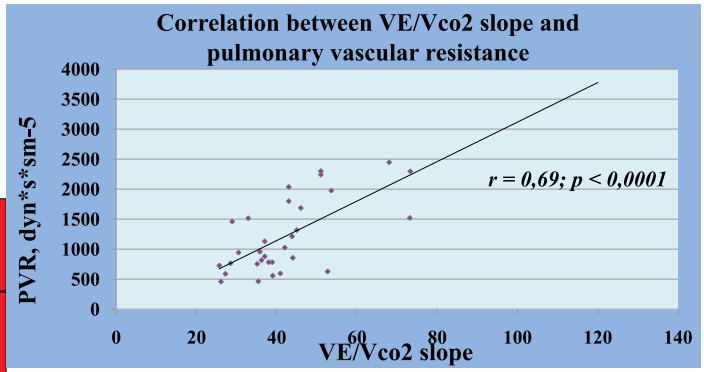
IPAH – idiopathic PAH, CHD – congenital heart diseases, CTD- connective tissue diseases, 6MWT- 6-minute walking test, FC (WHO)- functional class according to the World Health Organization classification, RA- right atrium, RV BD - right ventricular basal diameter, IVC –inferior vena cava, Vo2 peak- peak oxygen uptake, VE/Vco2 – ventilation equivalents for carbon dioxide, mPAP- mean pulmonary arterial pressure, mRAP- mean right atrial pressure, Svo2- mixed venous blood saturation, CI- cardiac index, PVR – pulmonary vascular resistance.

Parameters, that reflected the prognosis	Low risk <5%	Intermediate risk 5-10%	High risk >10%
CPET	VO2peak >15 ml/min/kg VE/VCO2 slope < 36	VO2peak 11-15 ml/min/kg VE/VCO2 slope 36-44,9	VO2peak <11 ml/min/kg VE/VCO2 slope ≥ 45



Results: The majority of pts (53%) had the high-risk of fatal events during 1 year (n=29), and 17 pts (31%) had the intermediate risk. After the CPET performing we found, that an additional 10 pts, who had been earlier in the intermediate risk, had a high risk of mortality during 1 year. 9 pts (16%) were belonged to the low risk , that was also confirmed by CPET data.





The significant negative correlation between Vo2peak and FC (WHO) was found (r=-0,68;p<0,0001). The significant positive correlation between Vo2peak and distance in 6MWT was revealed (r=0,68;p <0,0001). The VE/Vco2 slope value had significant positive correlation with PVR level (r=0,69;p<0,0001), RA area (r=0,5;p<0,003), mRAP (r=0,57;p<0,0012).

Conclusion: For the assessment of achieving therapy goals CPET is one of the reliable markers to reflect the PAH progression. The critical role of CPET in risk stratification in PAH pts should be emphasized.

Disclosure: The authors have no conflict of interests to declare.

Picture 2. The value of cardiopulmonary exercise test in assessment of the severity of pulmonary arterial hypertension patients