ORIGINAL ARTICLE

The impact of the new World Symposium on Pulmonary Hypertension definition of pulmonary hypertension on the prevalence of pre-capillary pulmonary hypertension

Dünya Pulmoner Hipertansiyon Kongresi yeni pulmoner hipertansiyon tanımlamasının pre-kapiller pulmoner hipertansiyon prevalansına etkisi

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ABSTRACT

Objective: Since the first World Symposium on Pulmonary Hypertension (WSPH; Geneva, 1973), pulmonary hypertension (PH) has been defined as a mean pulmonary artery pressure (mPAP) ≥25 mm Hg measured at right heart catheterization (RHC) while at rest in the supine position. At the 6th WSPH congress (Nice, 2018), a new proposal was presented defining pre-capillary PH as mPAP >20 mm Hg, with pulmonary arterial wedge pressure (PAWP) <15 mm Hg, and pulmonary vascular resistance (PVR) >3 WU. The aim of this study was to investigate the impact of the new definition of PH on the number of pre-capillary PH patients.

Methods: The results of RHC performed with various clinical indications between 2017 and 2018 were analyzed. The 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) and the 6th WSPH congress PH definitions were used to identify PH patients.

Results: Fifty-eight RHC procedures were performed in our hospital in a 1-year period. Most were performed with a suspicion of PH (n=52). The remainder (n=6) were performed with indications of valvular heart disease or left heart disease. There were 40 females (69%) and 18 males (31%). The mean age was 53.3±16.6 years. The RHC results revealed a mean PAP of 36.4±16.4 mm Hg, PAWP of 12.6±3.9 mm Hg, and PVR of 4.9±4.4 WU. Forty-three of 58 patients (74.1%) were classified as pre-capillary PH according to the ESC/ERS PH guideline, whereas 50 of 58 patients (86.2%) had pre-capillary PH according to the new WSPH definition.

Conclusion: The results of this study indicated that the impact of the new definition of PH on the number of pre-capillary PH patients identified was greater than the predicted <10%.

ÖZET

Amaç: 1. Dünya Pulmoner Hipertansiyon Kongresi'nde (Genova, 1973) pulmoner hipertansiyon (PH), sağ kalp kateteri ile istirahatte supin pozisyonunda ölçülen ortalama pulmoner arter basıncının (PAB) ≥25 mm Hg olması olarak tanımlandı. Bu sene düzenlenen 6. Dünya Pulmoner Hipertansiyon Kongresi'nde (Nice, 2018) ise bu tanımın, ortalama PAB >20 mm Hg, pulmoner kapiller uç basıncı (PKUB) <15 mm Hg ve pulmoner vasküler direnç (PVR) >3 WU olarak güncellenmesi önerildi. Bu çalışmada, yeni tanımlamayla birlikte pre-kapiller PH hasta sayımızdaki artış miktarını araştırmayı amaçladık.

Yöntemler: 2017–2018 yılları arasında, hastanemizde çeşitli endikasyonlarla yapılan sağ kalp kateteri raporları tarandı. Hem 2015 Avrupa Kardiyoloji ve Solunum Derneği (ESC/ERS) hem de 6. Dünya Pulmoner Hipertansiyon Kongresi PH tanı kriterleri kullanılarak, PH tanısı alan hasta sayısı (%) hesaplandı.

Bulgular: Bir yıllık periyotta hastanemizde 58 hastaya sağ kalp kataterı uygulandı. İşlemlerin çoğunluğu PH ayırıcı tanısı endikasyonuyla (n=52) uygulandı. Diğer endikasyonlar arasında kalp kapak hastalığı ve sol kalp hastalıkları yer almaktaydı (n=6). Hastaların 40'ı kadın (%69), 18'i erkek (%31) hastalardan oluşmaktaydı. Çalışma grubunun ortalama yaşı 53.3±16.6 idi. Sağ kalp kataterinde ortalama PAB 36.4±16.4 mm Hg, ortalama PKUB: 12.6±3.9 ve ortalama PVR: 4.9±4.4 WU olarak saptandı. 2015 ESC ve ERS PH kılavuz tanı kriterlerine göre PH tanısı alan hasta sayısı 43/58 (%74.1) iken, bu oran 6. Dünya Pulmoner Hipertansiyon Kongresi PH tanı kriterlerine göre 50/58 (%86.2) olarak saptandı.

Sonuç: 6. Dünya PH Kongresinde yeni hemodinamik pre-kapiller PH tanımlamasıyla hasta sayısındaki artışın <%10 olacağı ön görülürken, bizim çalışmamızda bu artış daha belirgin (%12.1) olarak saptandı.

Received: January 01, 2019 *Accepted:* January 12, 2019

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Pulmonary hypertension (PH) is defined as an increase in mean pulmonary artery pressure (mPAP) ≥25 mm Hg at rest as assessed using right heart catheterization (RHC).[1] The term pulmonary arterial hypertension (PAH) describes a disorder in a group of PH patients hemodynamically characterized by the presence of pre-capillary PH, which is defined by a pulmonary arterial wedge pressure (PAWP) ≤15 mm Hg and a pulmonary vascular resistance (PVR) >3 WU in the absence of other causes of pre-capillary PH, such as PH due to lung disease, chronic thromboembolic PH (CTEPH), or other rare diseases.[1]

PAH is characterized by remodeling of the small pulmonary arteries, leading to a progressive increase in PVR and right ventricular failure.[2] Since the 1st World Symposium of Pulmonary Hypertension (WSPH), PH has been defined as an mPAP ≥25 mm Hg measured using RHC at rest in the supine position. This definition remained unchanged until the 2018 WSPH. The accumulated data of healthy individuals suggested that a normal mPAP at rest is 14.0±3.3 mm Hg.[3] Moreover, in various conditions, an mPAP >20 mm Hg has been shown to be associated with an increased risk of mortality, although it has never been demonstrated that decreasing PAP improves survival. This mild increase in PAP could simply be a marker of the severity of underlying disease. A task force of the 6th WSPH suggested that an acceptable definition of pre-capillary PH could be mPAP >20 mm Hg, PAWP <15 mm Hg, and PVR >3 WU.[4,5]

It was highlighted at the 6th WSPH that the anticipated impact of the new definition on the number of pre-capillary PH patients identified would be low, with preliminary data suggesting an increase <10%. The objective of this study was to investigate the impact of the new definition on the number of pre-capillary PH patients identified at a single institution.

METHODS

Patients who underwent RHC with various clinical indications between 2017 and 2018 were included in the present study. Most often, the clinical indication was a differential diagnosis of PH, while RHC was also performed for indications of left heart disease and valvular heart disease. Patient demographics, clinical history details, and comorbidities were recorded from medical reports. Hemodynamic data (mPAP, PAWP, PVR) were collected from RHC reports. After evaluation of the RHC reports, patients with a final diagnosis of PAH were included in final analysis. Pre-capillary PH is defined as an mPAP ≥25 mm Hg, PAWP ≤15 mm Hg and PVR >3 WU according to the 2015 ESC/ERS PH Guideline,[1] while the 6th WSPH definition is an mPAP >20 mm Hg, PAWP <15 mm Hg, and PVR >3 WU.[4,5] Both definitions were used to define PAH patients for this study to examine the difference.

Abbreviations:

CTEPH	*Chronic thromboembolic pulmonary hypertension*
ESC	*European Society of Cardiology*
ERS	*European Respiratory Society*
mPAP	*Mean pulmonary arterial pressure*
PAH	*Pulmonary arterial hypertension*
PAP	*Pulmonary arterial pressure*
PAWP	*Pulmonary arterial wedge pressure*
PH	*Pulmonary hypertension*
PVD	*Pulmonary vascular disease*
PVR	*Pulmonary vascular resistance*
RHC	*Right heart catheterization*
TR	*Tricuspid regurgitation*
WSPH	*World Symposium on Pulmonary Hypertension*

Statistical analysis

Statistical analyses were performed using SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean±SD or median (minimum-maximum) and percentages were used for categorical variables. The Kolmogorov-Smirnov test was used to identify normal distribution of variables. Student's t-test or the Mann-Whitney U-test was used to compare continuous variables, and a chi square test was used to compare categorical data. A p value <0.05 was considered significant.

RESULTS

Fifty-eight RHC tests were performed at our center during the 1-year study period. Most of the procedures were performed with a suspicion of pre-capillary PH (n=52, 90%). The other indications were PH due to valvular heart disease (n=2: 1 patient with aortic stenosis and 1 with mitral stenosis, 3%) and PH due to left heart disease (n=4, 7%). All of the patients who underwent RHC (n=58) had a tricuspid regurgitation (TR) velocity of more than 2.8 m/second on transthoracic echocardiography. Among the patients with suspected pre-capillary PH, most (n=25) had a clinical suspicion of idiopathic PAH. Among the remaining 27 patients in this group, 20 patients had repaired or unrepaired congenital heart disease, 5 patients had a

previous history of pulmonary embolism, and 2 had systemic sclerosis. Three of 4 patients who had left heart disease were diagnosed with heart failure with reduced ejection fraction and 1 with heart failure with preserved ejection fraction. Figure 1 illustrates the distribution of clinical indications for RHC. Five patients were excluded due to missing hemodynamic data.

There were 40 female (69%) and 18 male (31%) patients, which is consistent with the typical female predominance in PAH. The mean age of study population was 53.3±16.6 years.

The RHC results revealed a mean PAP of 36.4±16.4 mm Hg, a mean PAWP of 12.6±3.9 mm Hg, and a mean PVR of 4.9±4.4 WU. Patients who had a PAWP measurement in the grey zone (PAWP 13–15 mm Hg) were given a fluid challenge test with 500 mL of saline over 5 minutes. None of the patients developed an abnormal response, defined as increasing PAWP >15 mm Hg. Just 1 patient had a positive response to acute vasodilator testing, which was accepted as a positive response of reduction of mPAP ≥10 mm Hg to reach an absolute mPAP value ≤40 mm Hg (increased or unchanged cardiac output). The acute vasodilator test was performed with iloprost. Table 1 shows the demographic and hemodynamic characteristics of the study population.

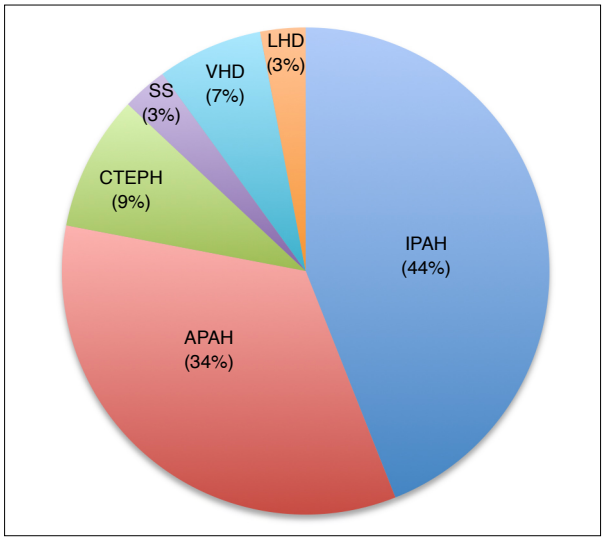

Figure 1. An illustration of the distribution of clinical indications for right heart catheterization. APAH-CHD: Pulmonary arterial hypertension associated with congenital heart disease; CTEPH: Chronic thromboembolic pulmonary hypertension; IPAH: Idiopathic pulmonary arterial hypertension; LHD: Left heart disease; SS: Systemic sclerosis; VHD: Valvular heart disease.

Table 1. Demographic and hemodynamic characteristics of the study population

Characteristics	n	%	Mean±SD
Age (years)			53.3±16.6
Female	40	61	
Male	18	39	
mPAP (mm Hg)			36.4±16.4
Mean PAWP (mm Hg)			12.6±3.9
Mean PVR (WU)			4.9±4.4
Positive VR	1	1.7	

mPAP: Mean pulmonary arterial pressure; PAWP: Pulmonary arterial wedge pressure; PVR: Pulmonary vascular resistance; VR: Vasoreactivity.

While 43 of 58 patients (74.1%) had pre-capillary PH according to the 2015 ESC/ERS PH guideline, when the 6th WSPH congress PH definition was used, 50 of 58 patients (86.2%) had pre-capillary PH. The impact of the new definition was greater than expected (12.1%). According to the new definition, 7 additional patients were diagnosed as pre-capillary PH. These patients had an mPAP 20–25 mm Hg, but a PVR >3 WU in these patients constituted evidence of pulmonary vascular disease. Among these 7 patients, 3 were diagnosed with idiopathic PAH, 2 were diagnosed as PAH associated with congenital heart disease, 1 was diagnosed as CTEPH, and 1 was diagnosed as PAH associated with systemic sclerosis. Six of 8 patients who were not diagnosed as pre-capillary PH had valvular heart disease or left heart disease. They had combined pre- and post-capillary PH defined as an mPAP >25 mm Hg, PVR >3 WU, and a PAWP >15 mm Hg. The other 2 patients had an mPAP 29±10.9 mm Hg, mean PVR 1.9±0.8 WU, and a mean PAWP 13.7±7.0 mm Hg. Although their mPAP was high, the PVR values were not high enough for a diagnosis of pre-capillary PH.

DISCUSSION

Since the 1st WSPH, PH has been defined as an mPAP >25 mm Hg measured using RHC in the supine position at rest. However, data in healthy individuals now suggest that a normal mPAP at rest is 14.0±3.3 mm Hg.[3] An mPAP >20 mm Hg was suggested as the upper limit of a normal value (mean value+2 SD). It

is important to emphasize that an mPAP >20 mm Hg does not define a disease per se, but only indicates an abnormal increase in pressure. In different conditions, an mPAP >20 mm Hg is associated with an increased risk of mortality; however, it has never been demonstrated that decreasing PAP improves survival.[6–9] This mild increase in PAP could be simply a marker of the severity of underlying disease.

In this study, there were 40 females (69%) and 18 males (31%), which is consistent with the female predominance seen in PAH. The female:male ratio was 1.7 in the REVEAL registry (Registry to Evaluate Early and Long-term PAH Disease Management),[10] 1.5 in the COMPERA registry,[11] 1.9 in a French registry,[12] and 1.9 in the SIMURG registry (Registry on Clinical Outcome and Survival in Pulmonary Hypertension Groups).[13] The mean age of our study population was 53.3±16.6 years. It was similar to that of the REVEAL registry (53±14 years)[4] and was higher than most other registries.[12–17]

An increase of mPAP can be the consequence of many conditions that may be managed differently and have different outcomes (increase in cardiac output, elevation of PAWP, left-to-right cardiac shunt, blood hyperviscosity, and pre-capillary PH). It is important to define the presence of pre-capillary PH because specific therapies have been shown to improve the outcome. The 6th WSPH recommended a decrease in the mPAP threshold to >20 mm Hg from ≥25 mm Hg, as well as including PAWP <15 mm Hg and PVR >3 WU to refine the definition of pre-capillary PH. The value of PVR >3 WU has been used in the definition of PAH since 2003 and in the hemodynamic criteria for the inclusion of PAH patients in most randomized, controlled trials. Moreover, there is accumulating data that in pre-capillary PH with an mPAP 21–24 mm Hg, the PVR is generally >3 WU. The definition allows for the identification of pulmonary vascular disease (PVD) at an earlier stage. Recent data from patients with scleroderma-associated PAH and patients with CTEPH support the idea of potentially initiating treatment for this population with a lower mPAP.[14–17] Conversely, the other side of this dilemma could be to undertreat some patients with an abnormal elevation of PAP but not meeting the classic definition of PH. Today, there is growing evidence that in some PVDs (mainly PAH-associated with systemic sclerosis, chronic thromboembolism, or chronic lung diseases), patients with even a modest elevation in mPAP (21–24 mm Hg) are symptomatic, have an exercise limitation, and may have a poor outcome. Nevertheless, a change in the hemodynamic definition of PH due to PVD does not imply a need for treatment for these additional patients, but highlights the importance of close monitoring in this population. Prospective trials are required to determine whether this PH population might benefit from specific management. Two cohorts with a mixed PH population have assessed the impact of this new definition in the number of pre-capillary PH patients: There was a 2% increase (1–3%) in the PH population in a Sao Paulo cohort and a 6% (5–7%) increase in a Giessen cohort.[18] The effect of the new definition was 12.1% in our study. The result may be related to the fact that our hospital is a tertiary cardiology center and patients with a high suspicion of PAH are referred for further examination. The result may be different in PAH centers other than cardiology clinics. Also, all of our patients had a TR velocity >2.8 m/second, which constitutes high clinical suspicion for PH. Left heart disease, valvular heart disease, and perioperative evaluation of patients who are candidates for lung and/or heart transplantation are the other common indications for RHC. In our study, those were the main indication for RHC in only a small number of patients, which constitutes a limitation.

Conclusion

It has been suggested that the threshold of the definition of PH be lowered to 20 mm Hg from 25 mm Hg. The impact of the new definition on the number of pre-capillary PH patients identified was thought to be low, with preliminary data suggesting an increase <10%. However, the impact of the new definition in our cohort was 12.1%, which was greater than expected. We believe the suggestion to lower the PH threshold from an mPAP of 25 mm Hg to 20 mm Hg will increase the number of patients diagnosed as pre-capillary PH.

Ethics Committee Approval: This study is retrospective. Ethics committee approval was not received as it was made before the adoption of the current law on the protection of personal information.

Peer-review: Externally peer-reviewed.

Conflict-of-interest: None.

Authorship contributions: CConcept: U.Y.S., M.S.K.; Design: U.Y.S.; Supervision: M.S.K., M.K.E., A.A.O.; Ma-

terials: U.Y.S., O.C.; Data: U.Y.S., O.C.; Analysis: U.Y.S.; Literature Search: U.Y.S.; Writing: U.Y.S.; Critical Revision: U.Y.S., M.S.K.

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Keywords: Hemodynamic; pre-capillary pulmonary hypertension; right heart catheterization; World Symposium on Pulmonary Hypertension.

Anahtar sözcükler: Hemodinami; pre-kapiller pulmoner hipertansiyon; sağ kalp kateteri; Dünya Pulmoner Hipertansiyon Kongresi.