# Balloon pulmonary angioplasty in the treatment of chronic thromboembolic pulmonary hypertension: recent advances and future perspectives

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**ABSTRACT**
Chronic thromboembolic pulmonary hypertension constitutes a significant late sequela of pulmonary embolism. It is defined by precapillary pulmonary hypertension with mismatched perfusion defects and pulmonary arterial lesions after at least 3 months of effective anticoagulation. Symptomatic patients who do not have pulmonary hypertension yet fulfill all other criteria are diagnosed with chronic thromboembolic disease. The treatment of chronic thromboembolic pulmonary hypertension is based on 3 pillars: pulmonary endarterectomy, pulmonary arterial hypertension–targeted medication, and balloon pulmonary angioplasty. Surgical pulmonary endarterectomy is the standard of care and can be performed in 2/3 of all patients. Targeted medication with or without balloon pulmonary angioplasty is reserved for inoperable patients or those with residual pulmonary hypertension after surgical treatment. Despite the lack of profound evidence, the treatment of chronic thromboembolic disease is similar to that of patients with pulmonary hypertension: pulmonary endarterectomy is offered to operable individuals, whereas balloon pulmonary angioplasty is considered in inoperable patients. Since therapeutic strategies are complex, and diagnostic and therapeutic procedures—demanding, treatment in a specialized, experienced center is mandatory.

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**Introduction** Up to 4% of all survivors of acute pulmonary embolism will develop chronic thromboembolic pulmonary hypertension (CTEPH).[1-3] In these patients, incomplete resolution with fibrotic alteration of the thrombotic material may be caused by inflammation, infection, thyroid dysfunction, irregular angiogenesis, and abnormal circulating phospholipids or fibrinogen.[4-9] Obstruction of at least 40% to 60% of the pulmonary arteries leads to the development of pulmonary hypertension (PH) with subsequent right heart impairment.[1] In addition, aggravating microvasculopathy may develop, which is currently explained by hyperperfusion and shear stress in the pulmonary vasculature. If left untreated, CTEPH has a dismal prognosis due to right heart and secondary multiorgan failure.[10,11]

Chronic thromboembolic pulmonary hypertension is the main representative of group 4 of the Nice classification of PH and is defined by symptomatic precapillary PH at rest with mismatched perfusion defects and pulmonary arterial lesions after effective anticoagulation lasting at least 3 months.[12-15] If all criteria are fulfilled, but the patient has no PH at rest, chronic thromboembolic disease (CTED) is diagnosed.[14] The incidence of CTED following pulmonary embolism remains unknown.

**Treatment algorithm** Lifelong anticoagulation is recommended for all patients with CTEPH or CTED. Additional treatments include diuretics or long-term oxygen therapy. The specific therapy of CTEPH is based on 3 methods: surgical pulmonary endarterectomy (PEA), pulmonary arterial hypertension–targeted medication, and interventional balloon pulmonary angioplasty (BPA). The therapeutic strategy has developed over the last 10 years in an interesting way. The European guidelines from 2009 recommended PEA as the standard treatment (level of evidence IC), while targeted medication might have been considered in inoperable patients (IIb/C), and BPA was not even mentioned.[16] In 2015, the European guidelines recommended PEA for operable CTEPH (IC), while targeted medication was recommended in inoperable patients or those with residual/recurrent PH after PEA (IB), and BPA might be considered in inoperable patients (IIb/C).[13] The most recent recommendation from 2019, derived from the "6th World Symposium on Pulmonary Hypertension," shows a pragmatically simplified therapeutic algorithm in comparison with the European guidelines from 2015, with PEA being the "treatment of choice" and targeted medication viewed as the first-line therapy in inoperable CTEPH patients "with or without" BPA.[17] It is undisputed that PEA is the only potentially curative treatment option for patients with CTEPH: complete removal of the obstructing material leads to a significant clinical and hemodynamic improvement and a distinct benefit for long-term survival.[18-23] Knowledge about the level of hemodynamic impairment and severe comorbidities as well as the availability of excellent imaging facilities and surgical expertise are of importance in the therapy decision-making process.[19,24] If pulmonary arterial lesions are located only in peripheral, subsegmental vessels, surgical treatment may not be possible. When in doubt, a second opinion should be considered.[13,15] Altogether, 1/3 of all patients with CTEPH are not amenable to PEA.[25] Specific medication is recommended in these inoperable patients, with secondary microvasculopathy being assumed to be the target and the rationale for medical therapy.[25] Currently, riociguat and treprostinil are approved for inoperable patients with CTEPH.[26,27] Residual or recurrent PH after PEA is another indication for targeted medication.

Balloon pulmonary angioplasty was developed to treat peripheral lesions in inoperable patients with CTEPH: the intervention was first described in 1988,[28] and the first series of 18 patients treated in the United States was presented in 2001.[29] Shortly thereafter, another case series from Germany was published.[30] Due to high complication and mortality rates, all programs were stopped and almost 10 years passed until the Japanese team demonstrated a refined concept:[31] Balloon pulmonary angioplasty was performed as a staged procedure with a limited number of treated pulmonary segments per session. This led to a distinct decrease in complications and mortality. The outcome was also very promising: several case series from Japan showed a significant improvement of pulmonary hemodynamics with a decrease in pulmonary vascular resistance of up to 65%.[32,33] Meanwhile, various centers around the world have published their initial results.[34-39] In TABLE 1, we summarized initial experiences beginning with the United States group in 2001, then presenting the Japanese registry (7 centers) and the first European groups. It becomes obvious that especially the hemodynamic improvement is usually less pronounced than in Japanese studies. This issue has been discussed earlier,[35] and possible explanations may be related to differences in experience levels, indications—due to various levels of expertise in PEA surgery and BPA, intervals between diagnosis and the first intervention, and characteristics of patient populations.

The therapeutic algorithm in CTEPH cannot be directly transferred to patients with CTED. Thorough evaluation and careful decision making are crucial in this specific group of patients; other explanations for patients' symptoms need to be ruled out by echocardiography and cardiopulmonary exercise testing.[14,17] Recently, exercise right heart catheterization was proposed as a method to detect irregular changes in exercise hemodynamics.[17] If CTED is diagnosed, surgical PEA may be offered, but the level of evidence is significantly lower than that of CTEPH.[18,40-42] The rate of inoperability in CTED remains unclear, and there are no studies available regarding the use of targeted medication. However, there has been some experience in the interventional treatment of inoperable patients with CTED: BPA was clinically beneficial,[43,44] and pulmonary hemodynamics showed an improvement in pulmonary arterial compliance,[43] which is assumed to be a relevant prognostic marker in patients with pulmonary arterial hypertension.[45]

**Balloon pulmonary angioplasty** Technically, the BPA intervention is similar in patients with CTEPH and those with CTED[31,35,43]: using a femoral or jugular venous access, a 6- to 8-Fr sheath is inserted into the central pulmonary artery, and the target segmental branch is intubated using differently angled guiding catheters. A guidewire crosses the lesion and balloon dilatation is subsequently performed. To avoid complications like reperfusion edema, the number of targeted pulmonary segments is attuned to the degree of PH. Nowadays, it is acknowledged that the most frequent (and clinically most relevant) complication is parenchymal hemorrhage, mostly caused by wire perforation. Therefore,

**TABLE 1** Initial results of balloon pulmonary angioplasty programs from various international centers [29,33-39]

| Study, country / region | Multicenter (yes / no) | Patients, n | Age, y, mean | Follow-up, m | Targeted medication, % | Change in mPAP, mm Hg, mean (SD) | Change in PVR, % | Lung injury, % | 30-day mortality, % | Long-term survival, % |
|---|---|---|---|---|---|---|---|---|---|---|
| Feinstein et al,[29] United States | No | 18 | 52 | 36 | 0 | 43 (12.1) to 33.7 (10.2) | NR | 61 | 5.6 | 89 at 39.2 months |
| Andreassen et al,[34] Norway | No | 20 | 60 | 51 | 10 | 45 (11) to 33 (10) | –33 | 35 | 10 | 85 at 51 months |
| Ogawa et al,[33] Japan | Yes | 308 | 62 | 101 | 72 | 43.1 (11) to 22.5 (5.4) | –66 | NR (per patient) | 2.6 | 94.5 at 36 months |
| Darocha et al,[39] Poland | No | 25 | 59 | NR | 76 | 51.7 (10.6) to 35 (9.1) | –47 | NR (per patient) | 0 | NR |
| Olsson et al,[35] Germany | Yes | 56 | 65 | 14 | 93 | 40 (12) to 33 (11) | –26 | 32 | 1.8 | NR |
| Brenot et al,[36] France | No | 154 | 63 | 42 | 62 | 43.9 (9.5) to 31.6 (9) | –46 | 46 | 2.2 | 97.3 at 12 months; 95.1 at 36 months |
| van Thor et al,[37] The Netherlands | No | 38 | 65 | 45 | 82 | 39.5 (11.6) to 30.6 (8.2) | –46 | NR (per patient) | 0 | NR |
| Hoole SP et al,[38] United Kingdom | No | 30 | 64 | 31 | 93 | 44.7 (11) to 34.4 (8.3) | –34 | NR (per patient) | 0 | NR |

Abbreviations: mPAP, mean pulmonary artery pressure; NR, not reported

floppy-tipped wires are mainly used with most cautious wire manipulation, especially in the periphery of the pulmonary vasculature.[46,47] Interestingly, in our own cohort (more than 1300 interventions), the use of short-term noninvasive ventilation to avoid dystelectasis after pulmonary hemorrhage significantly shortened hospital stay (median [interquartile range], 6 [4–9] versus 4 [4–5] days; $P = 0.015$) (unpublished data). Further, balloon size is slightly underestimated to avoid pulmonary artery rupture. The intervention is performed under fluoroscopy guidance, and numerous centers use digital subtraction angiography to document the postinterventional result [29-40] (FIGURE 1). Meanwhile, various refinements have been suggested such as the use of optical coherence tomography,[48] dyna–computed tomography,[49] as well as pressure wires and intravascular ultrasound.[50] Interestingly, frequent administration of contrast medium for BPA did not impair renal function.[51,52] Importantly, no data exist on the rate of restenosis after BPA. However, according to our and other centers' expertise, "there is no tendency towards restenosis [and] it is unnecessary to use stents."[53] Nevertheless, this specific issue necessarily needs further investigation.

For the evaluation of mid-term outcomes at 6 to 12 months after BPA, physical capacity (World Health Organization functional class, 6-minute walking distance), evaluation of quality of life, echocardiography, cardiopulmonary exercise test, oxygenation level, and pulmonary hemodynamics are usually used.[29-40,54] Additionally, blood serum biomarkers such as N-terminal fragment of the prohormone brain natriuretic peptide,[55] high-sensitivity cardiac troponin T,[56] growth differentiation factor 15, soluble suppression of tumorigenesis 2,[57] pregnancy-associated plasma protein A,[58] cartilage intermediate layer protein 1,[59] as well as cardiac magnetic resonance imaging[60] and electrocardiography[61] may be useful noninvasive diagnostic tools. The invasive measurement of pulmonary hemodynamics, not only at rest but also during exercise, offers a differentiated insight into the hemodynamic changes after BPA. Interestingly, even in patients without PH at rest after BPA, signs of exercise PH are detectable.[62,63]

Considering the promising short- to mid-term outcomes as well as the reduced complication and mortality rates, BPA appears to be an important and established treatment method for inoperable patients with CTEPH. The key limitation thus far is the lack of long-term results: there have been very few studies that explored the effects of BPA after a longer time period (eg, at around 4 years).[64,65] An international BPA registry is currently collecting data from approximately 500 patients (ClinicalTrials.gov identifier, NCT03245268). Furthermore, a randomized, controlled trial comparing targeted medication

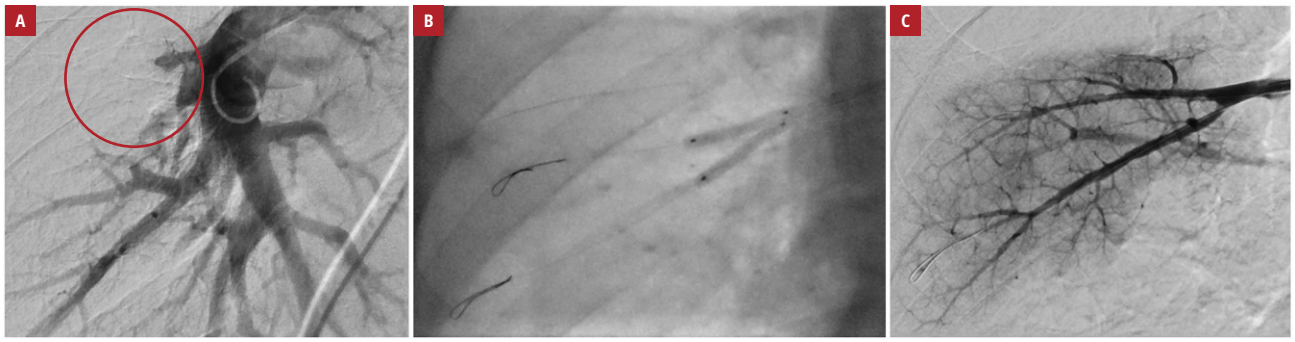


**FIGURE 1** Balloon pulmonary angioplasty in segment 4 of the right lung. A complete occlusion of the ostium of both subsegmental branches was initially observed (**A**; circle). Guidewires crossed the lesions and were navigated to both subsegmental arteries. Subsequently, a "kissing balloon" maneuver was performed (**B**). Postinterventional angiography revealed that the whole pulmonary segment was reperfused with a quick venous return (**C**).

(riociguat) with BPA is underway, but it has not been published yet (ClinicalTrials.gov identifier, NCT02634203). Both studies may influence future guideline recommendations. However, it appears reasonable to combine targeted medication and BPA in inoperable patients with CTEPH, since there are synergistic effects on clinical and hemodynamic outcomes; BPA was thereby more effective, but, as mentioned above, targeted medication has another rationale in CTEPH.[66-68] Other interesting multimodal approaches have been proposed: the combination of PEA and BPA in a single procedure[69] and the use of BPA in operated patients with residual PH after PEA.[70] Those hybrid procedures (PEA + BPA in a single session) are restricted to carefully selected patients with severe PH and operable disease on one side, while having peripheral disease in the contralateral lung. Such a procedure can be performed only in the most experienced high-volume centers. The combination of PEA with BPA in the further course is a long-term concept for patients with residual or recurrent CTEPH after surgery.

**Future perspectives** Future randomized, controlled trials may compare the effects of PEA and BPA in patients with subsegmental disease. Strict standardization of diagnostic, surgical, and interventional procedures in such trials will be of key importance: imaging quality as well as surgical and interventional expertise usually differ between centers. Another important aspect is cost-effectiveness, especially with regard to long-term, targeted medication after interventional therapy. Outcome parameters will need to be defined so that they indicate a patient's condition and prognosis as accurately as possible. Finally, the incidence of CTED after pulmonary embolism and larger trials on the treatment of CTED are certain to be of scientific interest.

## ARTICLE INFORMATION

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## REFERENCES

1 Pengo V, Lensing AWA, Prins MH, et al. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. N Engl J Med. 2004; 350: 2257-2264.

2 Klok FA, van Kralingen KW, van Dijk APJ, et al. Prospective cardiopulmonary screening program to detect chronic thromboembolic pulmonary hypertension in patients after acute pulmonary embolism. Haematologica. 2010; 95: 970-975.

3 Ende-Verhaar YM, Cannegieter SC, Von Noordegraaf A, et al. Incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: a contemporary view of the published literature. Eur Respir J. 2017; 49: 1 601 792.

4 Bonderman D, Jakowitsch J, Adlbrecht C, et al. Medical conditions increasing the risk of chronic thromboembolic pulmonary hypertension. Thromb Haemost. 2005; 93: 512-516.

5 Bonderman D, Jakowitsch J, Redwan B, et al. Role for staphylococci in misguided thrombus resolution of chronic thromboembolic pulmonary hypertension. Arterioscler Thromb Vasc Biol. 2008; 28: 678-684.

6 Zabini D, Nagaraj C, Stacher E, et al. Angiostatic factors in the pulmonary endarterectomy material from chronic thromboembolic pulmonary hypertension patients cause endothelial dysfunction. PLoS One. 2012; 7: e43793.

7 Alias S, Redwan B, Panzenbock A, et al. Defective angiogenesis delays thrombus resolution: a potential pathogenetic mechanism underlying chronic thromboembolic pulmonary hypertension. Arterioscler Thromb Vasc Biol. 2014; 34: 810-819.

8 Morris TA, Marsh JJ, Chiles PG, et al. High prevalence of dysfibrinogenemia among patients with chronic thromboembolic pulmonary hypertension. Blood. 2009; 114: 1929-1936.

9 Krieg VJ, Hobohm L, Liebetrau C, et al. Risk factors for chronic thromboembolic pulmonary hypertension - Importance of thyroid disease and function. Thromb Res. 2020; 185: 20-26.

10 Lang IM, Pesavento R, Bonderman D, Yuan JX. Risk factors and basic mechanisms of chronic thromboembolic pulmonary hypertension: a current understanding. Eur Respir J. 2013; 41: 462-468.

11 Riedel M, Stanek V, Widimsky J, Prerovsky I. Longterm follow-up of patients with pulmonary thromboembolism. Late prognosis and evolution of hemodynamic and respiratory data. Chest. 1982; 81: 151-158.

12 Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019; 53: 1801913.

13 Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint 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: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016; 37: 67-119.

14 Wilkens H, Konstantinides S, Lang I, et al. Chronic thromboembolic pulmonary hypertension: recommendations of the Cologne Consensus Conference 2016. Dtsch Med Wochenschr. 2016; 141: 62-69.

15 Wilkens H, Konstantinides S, Lang IM, et al. Chronic thromboembolic pulmonary hypertension (CTEPH): updated recommendations from the Cologne Consensus Conference 2018. Int J Cardiol. 2018; 272: 69-78.

16 Galiè N, Hoeper MM, Humbert 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.

17 Kim NH, Delcroix M, Jais X, et al. Chronic thromboembolic pulmonary hypertension. Eur Respir J. 2019; 53: 1801915.

18 Madani MM, Auger WR, Pretorius V, et al. Pulmonary endarterectomy: recent changes in a single institution's experience of more than 2,700 patients. Ann Thorac Surg. 2012; 94: 97-103.

19 Mayer E, Jenkins D, Lindner J, et al. Surgical management and outcome of patients with chronic thromboembolic pulmonary hypertension: results from an international prospective registry. J Thorac Cardiovasc Surg. 2011; 141: 702-710.

20 Delcroix M, Lang I, Pepke-Zaba J, et al. Long-term outcome of patients with chronic thromboembolic pulmonary hypertension: results from an international prospective registry. Circulation. 2016; 133: 859-871.

21 Cannon JE, Su L, Kiely DG, et al. Dynamic risk stratification of patient long-term outcome after pulmonary endarterectomy: results from the United Kingdom National Cohort. Circulation. 2016; 133: 1761-1771.

22 Hoeper MM, Madani MM, Nakanishi N, et al. Chronic thromboembolic pulmonary hypertension. Lancet Respir Med. 2014; 2: 573-582.

23 Archibald CJ, Auger WR, Fedullo PF, et al. Long-term outcome after pulmonary thromboendarterectomy. Am J Respir Crit Care Med. 1999; 160: 523-528.

24 Jenkins D, Madani M, Fadel E, et al. Pulmonary endarterectomy in the management of chronic thromboembolic pulmonary hypertension. Eur Respir Rev. 2017; 26: 160111.

25 Pepke-Zaba J, Delcroix M, Lang I, et al. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. Circulation. 2011; 124: 1973-1981.

26 Ghofrani HA, D'Armini AM, Grimminger F, et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. N Engl J Med. 2013; 369: 319-329.

27 Sadushi-Kolici R, Jansa P, Kopec G, et al. Subcutaneous treprostinil for the treatment of severe non-operable chronic thromboembolic pulmonary hypertension (CTREPH): a double-blind, phase 3, randomised controlled trial. Lancet Respir Med. 2019; 7: 239-248.

28 Voorburg JA, Cats VM, Buis B, Bruschke AV. Balloon angioplasty in the treatment of pulmonary hypertension caused by pulmonary embolism. Chest. 1988; 94: 1249-1253.

29 Feinstein JA, Goldhaber SZ, Lock JE, et al. Balloon pulmonary angioplasty for treatment of chronic thromboembolic pulmonary hypertension. Circulation. 2001; 103: 10-13.

30 Pitton MB, Herber S, Mayer E, Thelen M. Pulmonary balloon angioplasty of chronic thromboembolic pulmonary hypertension (CTEPH) in surgically inaccessible cases. Rofo. 2003; 175: 631-634.

31 Mizoguchi H, Ogawa A, Munemasa M, et al. Refined balloon pulmonary angioplasty for inoperable patients with chronic thromboembolic pulmonary hypertension. Circ Cardiovasc Interv. 2012; 5: 748-755.

32 Sugimura K, Fukumoto Y, Satoh K, et al. Percutaneous transluminal pulmonary angioplasty markedly improves pulmonary hemodynamics and long-term prognosis in patients with chronic thromboembolic pulmonary hypertension. Circ J. 2012; 76: 485-488.

33 Ogawa A, Satoh T, Fukuda T, et al. Balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension: results of a multicenter registry. Circ Cardiovasc Qual Outcomes. 2017; 10: e004029.

34 Andreassen AK, Ragnarsson A, Gude E, et al. Balloon pulmonary angioplasty in patients with inoperable chronic thromboembolic pulmonary hypertension. Heart. 2013; 99: 1415-1420.

35 Olsson KM, Wiedenroth CB, Kamp JC, et al. Balloon pulmonary angioplasty for inoperable patients with chronic thromboembolic pulmonary hypertension: the initial German experience. Eur Respir J. 2017; 49: 1602409.

36 Brenot P, Jaïs X, Taniguchi Y, et al. French experience of balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension. Eur Respir J. 2019; 53: 1802095.

37 van Thor MCJ, Lely RJ, Braams NJ, et al. Safety and efficacy of balloon pulmonary angioplasty in chronic thromboembolic pulmonary hypertension in the Netherlands. Neth Heart J. 2020; 28: 81-88.

38 Hoole SP, Coghlan JG, Cannon JE, et al. Balloon pulmonary angioplasty for inoperable chronic thromboembolic pulmonary hypertension: the UK experience. Open Heart. 2020; 7: e001144.

39 Darocha S, Pietura R, Pietrasik A, et al. Improvement in quality of life and hemodynamics in chronic thromboembolic pulmonary hypertension treated with balloon pulmonary angioplasty. Circ J. 2017; 81: 552-557.

40 Taboada D, Pepke-Zaba J, Jenkins DP, et al. Outcome of pulmonary endarterectomy in symptomatic chronic thromboembolic disease. Eur Respir J. 2014; 44: 1635-1645.

41 van Kan C, van der Plas MN, Reesink HJ, et al. Hemodynamic and ventilatory responses during exercise in chronic thromboembolic disease. J Thorac Cardiovasc Surg. 2016; 152: 763-771.

42 Guth S, Wiedenroth CB, Rieth A, et al. Exercise right heart catheterisation before and after pulmonary endarterectomy in patients with chronic thromboembolic disease. Eur Respir J. 2018; 52: 1800458.

43 Wiedenroth CB, Olsson KM, Guth S, et al. Balloon pulmonary angioplasty for inoperable patients with chronic thromboembolic disease. Pulm Circ. 2018; 8: 2045893217753122.

44 Inami T, Kataoka M, Kikuchi H, et al. Balloon pulmonary angioplasty for symptomatic chronic thromboembolic disease without pulmonary hypertension at rest. Int J Cardiol. 2019; 289: 116-118.

45 Mahapatra S, Nishimura RA, Sorajja P, et al. Relationship of pulmonary arterial capacitance and mortality in idiopathic pulmonary arterial hypertension. J Am Coll Cardiol. 2006; 47: 799-803.

46 Ejiri K, Ogawa A, Fujii S, et al. Vascular injury is a major cause of lung injury after balloon pulmonary angioplasty in patients with chronic thromboembolic pulmonary hypertension. Circ Cardiovasc Interv 2018; 11: e005884.

47 Kurzyna M, Darocha S, Pietura R, et al. Changing the strategy of balloon pulmonary angioplasty resulted in a reduced complication rate in patients with chronic thromboembolic pulmonary hypertension. A single-centre European experience. Kardiol Pol. 2017; 75: 645-654.

48 Araszkiewicz A, Jankiewicz S, Łanocha M, et al. Optical coherence tomography improves the results of balloon pulmonary angioplasty in inoperable chronic thrombo-embolic pulmonary hypertension. Postepy Kardiol Interwencyjnej. 2017; 13: 180-181.

49 Lin JL, Chen HM, Lin FC, et al. Application of DynaCT angiographic reconstruction in balloon pulmonary angioplasty. Eur Radiol. 2020; 30: 6950-6957.

50 Roik M, Wretowski D, Łabyk A, et al. Refined balloon pulmonary angioplasty driven by combined assessment of intra-arterial anatomy and physiology-Multimodal approach to treated lesions in patients with non-operable distal chronic thromboembolic pulmonary hypertension-Technique, safety and efficacy of 50 consecutive angioplasties. Int J Cardiol. 2016; 203: 228-235.

51 Kriechbaum SD, Wiedenroth CB, Hesse ML, et al. Development of renal function during staged balloon pulmonary angioplasty for inoperable chronic thromboembolic pulmonary hypertension. Scand J Clin Lab Invest. 2019; 79: 268-275.

52 Darocha S, Banaszkiewicz M, Pietrasik A, et al. Changes in estimated glomerular filtration after balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension. Cardiorenal Med. 2020; 10: 22-31.

53 Kurzyna M, Darocha S, Koteja A, et al. Balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension. Postepy Kardiol Interwencyjnej. 2015; 11: 1-4.

54 Darocha S, Pietura R, Pietrasik A, et al. Improvement in quality of life and hemodynamics in chronic thromboembolic pulmonary hypertension treated with balloon pulmonary angioplasty. Circ J. 2017; 81: 552-557.

55 Kriechbaum SD, Wiedenroth CB, Wolter JS, et al. N-terminal pro-B-type natriuretic peptide for monitoring after balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension. J Heart Lung Transplant. 2018; 37: 639-646.

56 Kriechbaum SD, Wiedenroth CB, Keller T, et al. Dynamics of high-sensitivity cardiac troponin T during therapy with balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension. PLoS One. 2018; 13: e0204683.

57 Kriechbaum SD, Wiedenroth CB, Peters K, et al. Galectin-3, GDF-15, and sST2 for the assessment of disease severity and therapy response in patients suffering from inoperable chronic thromboembolic pulmonary hypertension. Biomarkers. 2020; 25: 578-586.

58 Kriechbaum SD, Rudolph F, Wiedenroth CB, et al. Pregnancy-associated plasma protein A - a new indicator of pulmonary vascular remodeling in chronic thromboembolic pulmonary hypertension? Respir Res. 2020; 21: 204.

59 Keranov S, Dörr O, Jafari L, et al. CILP1 as a biomarker for right ventricular maladaptation in pulmonary hypertension. Eur Respir J. 2020; 1901192.

60 Roller FC, Kriechbaum S, Breithecker A, et al. Correlation of native T1 mapping with right ventricular function and pulmonary haemodynamics in patients with chronic thromboembolic pulmonary hypertension before and after balloon pulmonary angioplasty. Eur Radiol. 2019; 29: 1565-1573.

61 Piłka M, Darocha S, Banaszkiewicz M, et al. The evolution of electrocardiographic signs of right ventricular overload after balloon pulmonary angioplasty in chronic thromboembolic pulmonary hypertension. Pol Arch Intern Med. 2019; 129: 451-459.

62 Wiedenroth CB, Rieth AJ, Kriechbaum S, et al. Exercise right heart catheterization before and after balloon pulmonary angioplasty in inoperable patients with chronic thromboembolic pulmonary hypertension. Pulm Circ. 2020; 10: 2045894020917884.

**63** Kikuchi H, Goda A, Takeuchi K, et al. Exercise intolerance in chronic thromboembolic pulmonary hypertension after pulmonary angioplasty. Eur Respir J. 2020; 56: 1901982.

**64** Aoki T, Sugimura K, Tatebe S, et al. Comprehensive evaluation of the effectiveness and safety of balloon pulmonary angioplasty for inoperable chronic thromboembolic pulmonary hypertension: long-term effects and procedure-related complications. Eur Heart J. 2017; 38: 3152-3159.

**65** Inami T, Kataoka M, Yanagisawa R, et al. Long-term outcomes after percutaneous transluminal pulmonary angioplasty for chronic thromboembolic pulmonary hypertension. Circulation. 2016; 134: 2030-2032.

**66** Wiedenroth CB, Ghofrani HA, Adameit MSD, et al. Sequential treatment with riociguat and balloon pulmonary angioplasty for patients with inoperable chronic thromboembolic pulmonary hypertension. Pulm Circ. 2018; 8: 2045894018783996.

**67** Aoki T, Sugimura K, Terui Y, et al. Beneficial effects of riociguat on hemodynamic responses to exercise in CTEPH patients after balloon pulmonary angioplasty – a randomized controlled study. Int J Cardiol Heart Vasc. 2020; 29: 100579.

**68** Kalra R, Duval S, Thenappan T, et al. Comparison of balloon pulmonary angioplasty and pulmonary vasodilators for inoperable chronic thromboembolic pulmonary hypertension: a systematic review and meta-analysis. Sci Rep. 2020; 10: 8870.

**69** Wiedenroth CB, Liebetrau C, Breithecker A, et al. Combined pulmonary endarterectomy and balloon pulmonary angioplasty in patients with chronic thromboembolic pulmonary hypertension. J Heart Lung Transplant. 2016; 35: 591-596.

**70** Araszkiewicz A, Darocha S, Pietrasik A, et al. Balloon pulmonary angioplasty for the treatment of residual or recurrent pulmonary hypertension after pulmonary endarterectomy. Int J Cardiol. 2019; 278: 232-237.