High prevalence of severe coronary artery disease in elderly patients with non-operable chronic thromboembolic pulmonary hypertension referred for balloon pulmonary angioplasty

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Abstract

Introduction: Balloon pulmonary angioplasty (BPA) is a new emerging catheter-based alternative treatment option for patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH).

Aim: To show that all elderly CTEPH patients referred for BPA are at higher risk of obstructive coronary artery disease and that, in daily practice, they should undergo invasive coronary angiography.

Material and methods: Eleven patients at the age of at least 65 years (6 males, 5 females, 77.2 ±5.9 years) with confirmed non-operable type II or type III CTEPH, considered for BPA, underwent elective coronary angiography. Severe obstructive coronary artery disease (CAD) was diagnosed when stenosis of left main coronary artery ≥ 50% or stenosis of ≥ 70% of epicardial arteries was angiographically confirmed. We also screened for CAD consecutive age- and sex-matched 114 PE survivors (52 males, 62 females, 74.8 ±7.2 years) with excluded CTEPH.

Results: Severe CAD was more frequent in elderly patients with non-operable type II or type III CTEPH candidates for BPA than in elderly acute PE survivors with excluded CTEPH (54.5% vs. 16.7%, $p < 0.01$), and therefore elderly CTEPH patients referred for BPA were at higher risk of CAD (OR = 5.9, 95% CI: 1.64–21.46, $p = 0.007$) when compared to elderly survivors after acute PE with excluded CTEPH.

Conclusions: All elderly CTEPH patients referred for BPA are at higher risk of severe CAD and should routinely undergo invasive coronary angiography before BPA.

Key words: chronic thromboembolic pulmonary hypertension, obstructive coronary artery disease, invasive coronary angiography, balloon pulmonary angioplasty.

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) can develop in approximately 1–3% of patients within 2 years of acute pulmonary embolism (PE) and mostly represents the consequences of failure of thrombus resolution [1–3]. Although venous thromboembolism and atherosclerosis have traditionally been considered as separate diseases, there is growing evidence that they share similar risk factors [4–7]. Moreover, it was reported that patients who survived acute PE episode are at an increased risk of subsequent arterial cardiovascular events including myocardial infarction and stroke [8]. Also a higher prevalence of coronary artery calcium was found in this group when compared to subjects without a history of venous thromboembolism [9]. Since chronic coronary artery disease (CAD) results from a long lasting exposure to risk factors that are also significant for PE, it seems plausible that CTEPH patients could be potentially at increased risk of CAD. Recently the International Registry on CTEPH reported 12% CAD incidence in CTEPH patients [10]. However, this group included patients in a wide age range, and most of them were not systematically screened for CAD. Importantly, there is a general agreement that elderly patients, in some centers older than 50 years, referred for pulmonary thromboendarterectomy (PEA) should be assessed with coronary angiography for CAD [11].

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Balloon pulmonary angioplasty (BPA) is an emerging therapeutic procedure for CTEPH in patients with distal thrombi or subjects too fragile for PEA [12, 13]. Although there is accumulating evidence on BPA application, its technique, efficacy and safety are still a matter of ongoing intensive research. The reported BPA mortality rate reached 3–10%, and most fatalities were caused by reperfusion pulmonary edema and irreversible right heart failure. However, currently there are no available data on the prevalence of CAD in elderly CTEPH patients referred for BPA.

Aim

We hypothesized that CAD is frequent in elderly patients with CTEPH considered for BPA, and that it may be more prevalent than in aged-matched patients after acute PE with excluded CTEPH.

Material and methods

Patient selection

Two hundred and eighty consecutive patients after a symptomatic episode of acute PE who were managed in our department and subsequently followed in our outpatient clinic and were anticoagulated for at least 3 months underwent detailed workup for CTEPH and CAD. All patients were subjected to clinical assessment and transthoracic echocardiography. Among patients with exertional dyspnea or echocardiographic signs indicating pulmonary hypertension suspected of CTEPH, it was confirmed in 12 patients. Moreover, among an additional 32 patients referred to our department with already suspected CTEPH, it was confirmed in another 12 patients. Thus, the group of 24 CTEPH patients was defined. However, 14 patients were not qualified for surgical PEA and were considered for BPA. Among them 11 patients were aged at least 65 years. All 114 patients aged above 65 years from the group of 268 PE survivors and excluded CTEPH underwent workup for CAD.

CTEPH diagnosis

Patients who showed at transthoracic echocardiography at least one of the following – tricuspid regurgitation velocity > 2.8 m/s, signs suggestive of pulmonary hypertension systolic septal flattening, right ventricular (RV) hypertrophy (RV free wall thickness > 6 mm), or W-pattern in the RV outflow curve or reported exertional dyspnea – were referred for further diagnostic tests including perfusion lung scintigraphy, and right heart catheterization (RHC). The diagnosis of CTEPH was defined as: abnormal lung scan with at least one segmental perfusion defect with normal chest X-ray, mean pulmonary artery pressure ≥ 25 mm Hg at rest in RHC, with pulmonary wedge pressure ≤ 15 mm Hg [14]. All patients during RHC underwent pulmonary angiography. Moreover, multidetector computed tomography (CT) angiography was performed in all subjects. Patients with diagnosed CTEPH type II or type III according to Jamieson's classification [15] were considered as candidates for BPA when they were found to be ineligible for PEA by a cardio surgeon or PEA expert.

Diagnosis of coronary artery disease

All patients with typical or atypical angina or with CAD risk factors (diabetes mellitus, hypertension) underwent noninvasive diagnosis of CAD: ECG exercise test, cardiac stress scintigraphy (single photon emission computed tomography (SPECT) with dipyridamole) or coronary angiography with 64-row multislice computed tomography (MSCT). The ECG exercise stress test was performed according to the Bruce or modified Bruce protocol with the Cambridge Heart system in patients with low pretest CAD probability. It was considered to indicate CAD when ECG abnormality consists of a horizontal or down-sloping ST-segment depression ≥ 0.1 mV, persisting for at least 0.06–0.08 s after the J-point, in two or more ECG leads and/or symptom(s) and sign(s) of ischemia were observed during or after the test. The SPECT or MSCT was performed in patients with intermediate pretest probability of CAD or when the ECG stress test was impossible to perform or to interpret or its result was inconclusive. Single photon emission computed tomography was considered to indicate CAD when myocardial perfusion abnormalities, increased uptake of the myocardial perfusion and transient ischemic dilatation and reduced post-stress ejection fraction were observed. Multislice computed tomography was considered to indicate the presence of obstructive CAD when significant lesion(s) were found in large and proximal coronary arteries. Patients with typical angina in at least class 2 of Canadian Cardiovascular Society (CCS) during follow-up, or with suspected acute coronary syndrome, or with results of a noninvasive test indicating high risk of major cardiac adverse events (MACE) were referred for invasive coronary angiography. Obstructive CAD was angiographically diagnosed in patients showing stenosis of the left main coronary artery of at least 50% or stenosis of at least 70% of epicardial arteries. The hemodynamic significance of coronary artery stenosis of moderate stenosis was determined with fractional flow reserve (FFR) with a cut-off point < 0.8. Coronary artery disease was also diagnosed in patients who experienced an acute coronary syndrome managed invasively or when medical records including ECG tracing and echocardiography-confirmed myocardial infarction.

All patients with CTEPH aged ≥ 65 years considered for invasive CTEPH therapy also underwent invasive coronary angiography, and CAD was diagnosed according to criteria specified above.

Statistical analysis

This is a prospective observational cohort study. Data described by a normal distribution are expressed as the

mean followed by their standard deviation. Parameters without this distribution are expressed as the median with the range. Student's or Mann-Whitney's tests were used for comparisons between two groups, while comparisons between more than two groups were performed using ANOVA or Kruskal-Wallis tests. Fisher's test was used to compare discrete variables. Logistic regression analysis was used to calculate the risk of CAD. The odds ratio was calculated to assess the risk of CAD. Data were considered significant at $p < 0.05$. Statistica (StatSoft 10.0, Inc. 2010) software was used for statistical calculations. The protocol of this study was approved by the Local Bioethics Committee. All participating patients expressed their prior informed consent.

Results

We included consecutive 11 patients aged at least 65 years (5 females, 6 males, 77.2 ±5.9 years) with non-operable type II or type III CTEPH (Table I).

All of them underwent elective coronary angiography which revealed severe obstructive CAD in 6 of them (54.5%). Significant stenosis of the left main artery was detected in two of them, while in two others significant stenosis of proximal parts of the left descending artery was visualized. An angiographic characteristics of 11 elderly patients with CTEPH are presented in Table II.

In the group of consecutive age- and sex-matched 114 PE survivors at the age of at least 65 years (62 female, 52 male, aged 74.8 ±7.2 years) with excluded CTEPH, coronary angiography was performed in 12 of 114 patients, revealing obstructive CAD, and in 6 cases CAD was confirmed non-invasively. Moreover, 1 additional patient was diagnosed with CAD after ACS managed medically in whom regional LV akinesis/dyskinesis was detected at echocardiography. Thus, eventually CAD was detected in 19 (16.7%) cases. Whereas in 95 other patients from this group CAD was eventually excluded. Thus, in elderly patients with CTEPH disqualified from PEA CAD was significantly more frequent than in elderly after acute PE with excluded CTEPH (54.5% vs. 16.7%, $p < 0.01$, Figure 1). Interestingly, we found no differences in frequency of hyperlipidemia or statin treatment in elderly subjects

Table I. Clinical characteristics of patients at the age of at least 65 years with confirmed chronic thromboembolic pulmonary hypertension (CTEPH) or after pulmonary embolism and excluded CTEPH

Parameter	CTEPH (–) (n = 114)	*P*-value	CTEPH (+) (n = 11)
Age, mean ± SD [years]	74.8 ±7.2	0.51	77.2 ±5.9
Gender F/M	62/52 (male 46%)	0.75	5/6 (male 55%)
Hypertension, *n* (%)	109 (96)	1.0	11 (100)
Diabetes, *n* (%)	30 (26)	1.0	3 (27)
Hyperlipidemia (%) LDL > 135 mg% or statin treatment, *n* (%)	75 (66)	0.52	6 (55)
Plasma LDL [mg%]	122.5 ±41.1	< 0.05	79.4 ±29.3
History of ACS, *n* (%)	9 (8)	1.0	1 (9)

SD – standard deviation, F – female, M – male, LDL – low-density lipoprotein, ACS – acute coronary syndrome.

Table II. Angiographic characteristics of 11 elderly patients with chronic thromboembolic pulmonary hypertension

No.	Gender	Age [years]	RCA	LM	LAD	DB	CX	MB	CAD treatment	CTEPH treatment
1	F	81	50	n	75	n	n	n	PCI: LAD – 1 DES	BPA
2	M	71	n	n	n	n	n	n	MT	BPA
3	M	83	60	90	90	0	50	n	PCI: LM + LAD – 3 DES	BPA
4	F	81	70	n	50	0	n	n	FFR RCA > 0.8, FFR LAD > 0.8, MT	BPA
5	F	84	n	n	n	0	n	n	MT	BPA
6	F	69	50	n	75	50	n	n	PCI: LAD – 1 DES	BPA
7	M	76	n	n	60	n	n	n	FFR > 0.8, MT	BPA
8	M	70	70	n	50	n	CTO	70	2 PCI: OM – 1 DES, LAD – 2 DES	BPA
9	M	77	60	70	70	70	70	n	PCI: 1 DES LM + LAD	BPA
10	M	75	n	n	n	n	n	n	MT	MT
11	F	80	n	n	n	n	n	n	MT	MT

F – female, M – male, RCA – right coronary artery, LM – left main, LAD – left anterior descending artery, DB – diagonal branch, MB – marginal branch, PCI – percutaneous coronary intervention, DES – drug-eluting stent, CTO – chronic total occlusion, MT – medical treatment, FFR – fractional flow reserve, BPA – balloon pulmonary angioplasty, CX – circumflex artery, n – no stenosis, OM – obtuse marginal artery.

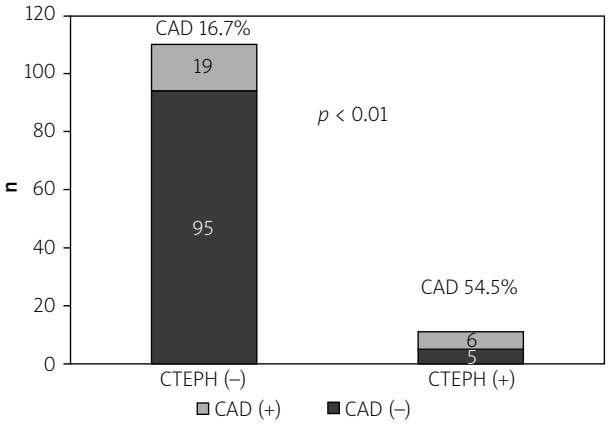

Figure 1. Prevalence of severe coronary artery disease (CAD) in elderly patients of at least 65 years after pulmonary embolism without (n = 114) and with (n = 11) chronic thromboembolic pulmonary hypertension (CTEPH)

with CTEPH and patients with excluded CTEPH. However, low-density lipoprotein (LDL) levels were significantly lower in the former (Table I).

Therefore, elderly CTEPH patients referred for BPA when compared to elderly subjects after acute PE with excluded CTEPH were at higher risk of CAD (OR = 5.9, 95% CI: 1.64–21.46, p = 0.007). All 5 patients with significant CAD and CTEPH underwent successful percutaneous coronary intervention (PCI) with drug-eluting stent implantations and several balloon pulmonary angioplasties. No significant complications occurred, and all treated patients are still alive.

Discussion

To our knowledge this is the first study reporting high prevalence of CAD in elderly patients with type II or III CTEPH ineligible for PEA and referred for BPA. In the group of 11 patients aged 77.2 ±5.9 years advanced coronary artery stenosis was angiographically diagnosed in 6 (54.5%) cases (Table II).

Importantly, significant stenosis of the left main artery was detected in two of them, while in two others significant stenosis of proximal parts of the left descending artery was visualized. These findings in 5 patients resulted in PCI performed before BPA therapy. Only in one patient with 70% stenosis in 3 segments of the RCA was PCI postponed. Interestingly, in none of the 6 CTEPH patients with severe coronary lesions has CAD been previously diagnosed. All observed patients reported severe dyspnea at exertion and significant functional impairment. Three patients were in WHO functional class III, 2 others in functional class IV, and only 1 in class II. None of them presented typical angina, but probably very limited physical activity due to advanced CTEPH prevented them from showing typical symptoms of exercise-induced ischemia while significant exertional dyspnea, a common clinical symptom of both diseases, was attributed to pulmonary hypertension in patients with already diagnosed CTEPH, impeded CAD suspicion, and eventually made CAD diagnosis difficult. This corresponds with observations indicating that only one-third of CTEPH patients with CAD confirmed at routine angiography before PEA gave a history suggestive for coronary disease [11]. These authors analyzed 1100 PEA cases and found that CABG was simultaneously performed in 83 (7.5%) patients. However, this group included patients in a wide age range, and patients requiring additional cardiac surgery were significantly older than patients requiring PEA only (68.1 ±8.1 vs. 50.4 ±14.2 years, p < 0.0001). The authors concluded that all elderly patients should be evaluated with coronary angiography prior to PEA [11]. Interestingly, in another group of 103 patients aged over 70 years who underwent PEA, CABG was performed simultaneously only in 16 (15.5%) cases [16]. Currently, patients older than 50 years referred for PEA in most centers are assessed with coronary angiography. In order to provide maximal safety of BPA we suggest performing coronary angiography in all elderly subjects considered for BPA. Interestingly, in our study CAD prevalence was significantly higher in elderly CTEPH patients than in 114 consecutive aged- and sex-matched patients after an acute PE episode managed in our institution in whom CTEPH was excluded (54.5 vs. 16.7%, p < 0.01). Therefore, elderly CTEPH patients referred for BPA were at higher risk of CAD with OR 5.9 (95% CI: 1.64–21.46, p = 0.007) than the latter. Of interest, a Japanese group reported safety and efficacy of BPA in 31 patients aged ≥ 65 years, although the authors did not perform any CAD screening [12]. Moreover, CAD has not been reported in Japanese CTEPH patients referred for pulmonary artery endarterectomy. Of importance, the prevalence of CAD in the Japanese general population is at least 2–3 fold lower than that of US [17]. Definitively, these data suggest ethnic differences between European and Japanese populations in the prevalence of cardiovascular disease. There is no evident explanation of increased CAD prevalence in elderly patients with non-major vessel CTEPH. We can suggest that similar mechanisms can lead to the persistence of non-resolved organized pulmonary artery thrombi and also can promote coronary artery disease [7]. Moreover, inflammation, systemic and local hypercoagulability, and endothelial injury may play integral mechanistic roles in the pathophysiology of atherosclerosis and venous thromboembolism [6]. Aortic stenosis is a recognized factor of CAD, and we suggest that elderly patients with CTEPH may also be at increased risk of CAD, which can be found in approximately 60% of transcatheter aortic valve implantation patients [18].

The major limitation of the current study is the limited number of elderly CTEPH patients referred for BPA. However, all of them underwent invasive angiography,

and the diagnostic criteria of CAD were very reliable. Coronary artery disease in patients with excluded CTEPH was arteriographically confirmed and invasively diagnosed in 12 patients and in 7 other patients CAD was confirmed non-invasively (SPECT, MSCT or exercise ECG test).

Conclusions

All elderly CTEPH patients referred for BPA are at higher risk of CAD and in our opinion should routinely undergo invasive coronary angiography before the BPA procedure.

Conflict of interest

The authors declare no conflict of interest.

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