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Long-Term Effects of Acute Pulmonary Embolism on Echocardiographic Doppler Indices and Functional Capacity

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Summary

Background and hypothesis: Hemodynamic and functional consequences of acute pulmonary embolism (APE) are believed to be reversible with antithrombotic treatment. To verify this hypothesis, we reassessed our patients at least 1 year after an episode of APE.

Methods: We compared echo Doppler indices and 6-min walking test parameters (6-MWT) of 36 patients (13 men, 23 women, age 66 ± 11 years), studied on average 3.1 ± 2.2 years after an acute episode of pharmacologically treated massive or submassive APE, with data of 30 age-matched subjects (12 men, 18 women, age 67 ± 12 years).

Results: At least 1 year after APE, right ventricular (RV) diameter remained increased in patients compared with controls (27 ± 2 vs. 23 ± 2 mm, $p < 0.001$). Also, acceleration time of pulmonary ejection (AcT) was markedly shorter (97 ± 19 vs. 123 ± 19 ms, $p < 0.001$) and the diameter of the pulmonary trunk was significantly larger in patients than in controls (21 ± 2.6 vs. 18 ± 2.2, $p < 0.001$). Although the mean value of the tricuspid valve peak systolic gradient (TVPG) in the APE group at follow-up was similar to that in controls, TVPG > 30 mmHg was recorded in three patients with APE (8.3%). There was no difference in the distance of 6-MWT between both groups; however, the mean desaturation after 6-MWT was higher in the APE group than in controls (3.04 ± 2.08 vs. 1.45 ± 0.69%, $p = 0.0005$).

Conclusions: Pharmacologic treatment of acute pulmonary embolism does not prevent mild persistent changes in morphology and function of the cardiovascular system. Despite normalization of pulmonary artery systolic pressure and similar exercise capacity, survivors of APE present signs suggesting RV dysfunction and/or its disturbed coupling to the pulmonary arterial bed, as well as ventilation to perfusion mismatch at exertion persisting long after the acute embolic episode.

Key words: acute pulmonary embolism, echocardiography, right ventricular dysfunction, 6-minute walking test

Introduction

Acute pulmonary embolism (APE) causes right ventricular (RV) pressure overload in approximately 50% of cases.[1–3] With antithrombotic treatment, resolution of echocardiographic signs of RV overload and normalization of the clinical status occur in the majority of patients with APE within several weeks.[4, 5] However, organized residuals of thromboemboli may persist in pulmonary arteries even despite adequate long-term anticoagulation. Development of chronic thromboembolic pulmonary hypertension was reported in some patients after APE.[4] However, there are limited data whether patients, after apparently having been successfully treated for APE, show any persistent impairment of pulmonary hemodynamics at rest or during exercise. Therefore, we assessed long-term exercise capacity and echo-Doppler indices describing RV function and its coupling to pulmonary arteries in patients after pharmacologically treated APE.

Materials and Methods

We reevaluated 36 patients (13 men, 23 women, mean age 66 ± 11) with APE confirmed at least 1 year previously. Only patients who presented signs of RV pressure overload at Doppler echocardiography at the time of diagnosis and before

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initiation of treatment were included. The group of 36 patients studied is a subgroup of 48 patients hospitalized with acute massive or submassive pulmonary embolism. During hospitalization eight patients died (17% in-hospital mortality); an additional four patients died during follow-up.

Patients with left ventricular systolic dysfunction, valvular heart disease, any pulmonary disease, or history of smoking were not included in the study. Acute pulmonary embolism was diagnosed by contrast-enhanced spiral computer tomography, which visualized thromboemboli in lobar and/or main pulmonary arteries, or by high-probability lung scintigraphy assessed according to Prospective Investigation Of Pulmonary Embolism (PIOPED) criteria.[6] The study population comprised only patients in whom the duration of symptoms suggestive for APE did not exceed 14 days because potential benefits of more aggressive therapy, particularly thrombolytic therapy, have been established in these patients. Patients with proven or clinically suspected recurrent APE during follow-up were not included in the study.

Acute pulmonary embolism was treated pharmacologically in all cases. In the acute phase, 30 patients received anticoagulation alone with unfractionated heparin dosed according to activated partial thromboplastin time (APTT) or weight-adjusted low molecular heparin administered subcutaneously. Thrombolysis was used in six patients and consisted of 2 h intravenous infusion of 1.5 million units of streptokinase, followed by intravenous heparin. The decision to start thrombolysis was based on the clinical status of a patient according to guidelines of the European Society of Cardiology.[7] Oral anticoagulation with International Normalized Ratio (INR) 2.0–3.0 was used for at least 6 months of treatment in all patients. As a control group we assessed 30 age- and gender-matched subjects (12 men, 18 women, mean age 67 ± 12 years). Special attention was given to the selection of the control group with the same profile of coexisting diseases (systemic hypertension, coronary artery disease, and diabetes mellitus) as observed in the study group. These subjects had no data for pulmonary disease and presented no echocardiographic evidence of structural heart disease.

All patients with APE underwent clinical and echocardiographic assessment at diagnosis. At follow-up at least 1 year after the acute episode, detailed examination including clinical assessment, chest x-ray, standard 12-lead electrocardiogram, Doppler echocardiography, and a 6-min walking test (6-MWT) was performed in all subjects. The same protocol of clinical assessment and accessory examinations, especially 6-MWT and transthoracic echocardiography, was applied to the control group.

Transthoracic Echocardiography

Echocardiographic studies were performed with Hewlett Packard Sonos 2000 (Andover, Md., USA) with 2.5–3.5 MHz transducers at the time of diagnosis and after follow-up. During examination, patients were in a left lateral position, and the dimensions of the right and left ventricles were measured in the parasternal long-axis view in late diastole defined by the R wave of the monitored electrocardiogram. After recording of the tricuspid valve peak systolic gradient (TVPG) with continuous-wave Doppler echocardiography, the tricuspid insufficiency pressure gradient was calculated according to the simplified Bernoulli equation. Acceleration time of pulmonary ejection (AcT) was measured using pulse-wave Doppler echocardiography with the sample volume placed in the RV outflow tract just below the pulmonary valve. Measurements were averaged over five consecutive heart cycles. The Tei index for the right ventricle was obtained by dividing the sum of RV isovolumetric contraction and relaxation time by RV ejection time, as has been described previously.[8]

Six-Minute Walking Test

The 6-MWT was performed on a level hallway surface and was supervised by a physician. The patients were instructed to cover the greatest distance possible during the allotted time, at a self-determined walking speed, pausing to rest as needed. Heart rate, blood pressure, and saturation of capillary blood were measured before and immediately after the test. The total distance covered in meters during the 6-MWT was recorded.

Statistical Analysis

The significance of the differences between the groups was compared by Student's *t*-test or Mann's U-test depending on the character of distribution. To assess the normalization of RV overload the *t*-test for paired data was used. Significance of the differences between categorical variables was established by Pearson's chi-square test with Yates' correction when needed. A p value of < 0.05 was considered statistically significant. Data in the tables are expressed as means ± standard deviations (SDs).

All participating subjects gave informed consent, and the protocol of the study was accepted by the local ethics committee.

Results

Follow-up assessment of patients with APE was performed at 3.1 ± 2.2 years. The clinical characteristics and coexisting diseases in APE and control groups are shown in Table I. There were no statistically significant differences in demographic parameters and coexisting diseases between the two groups. No important differences were found in long-term treatment of coexisting diseases such as essential hypertension, ischemic heart disease, or diabetes mellitus. The frequency of administration of beta blockers potentially affecting functional capacity was similar in the two groups.

Echocardiographic Data

At diagnosis, all patients with APE presented echocardiographic signs of RV overload (Table II), with dilated RV (32 ± 4 mm) and a mean RV/left ventricular (LV) ratio of (0.8 ±

TABLE I Clinical parameters and coexisting diseases in the acute pulmonary embolism follow-up group and in controls

Parameter	APE (n = 36)	Controls (n = 30)	p Value
Men (%)	13 (36)	12 (40)	NS
Women (%)	23 (64)	18 (60)	NS
Age (years)	66 ± 11	67 ± 12	NS
BMI (kg/m^2)	28 ± 3.9	27.2 ± 4.3	NS
Hypertension (%)	11 (31)	10 (30)	NS
Coronary artery disease (%)	4 (11)	3 (10)	NS
Diabetes mellitus (%)	2 (6)	2 (7)	NS
Use of beta blockers (%)	6 (17)	5 (17)	NS

Abbreviations: APE = acute pulmonary embolism, BMI = body mass index, NS = not significant.

TABLE II Echocardiographic parameters in patients with acute pulmonary embolism at the diagnosis and after follow-up

	APE (n = 36)	p Value [a]	APE follow-up (n = 36)	p Value [b]	Controls (n = 30)
RV (mm)	32 ± 4	< 0.001	27 ± 2	< 0.001	23 ± 2
RV/LV	0.8 ± 0.18	< 0.001	0.57 ± 0.1	< 0.001	0.49 ± 0.04
TVPG (mmHg)	48 ± 13	< 0.001	24 ± 8 (n = 13)	NS	24 ± 8 (n = 9)
AcT (ms)	58 ± 5	< 0.001	97±19	< 0.001	123±19
Tei index	0.39 ± 0.12	0.02	0.33 ± 0.06	0.03	0.30 ± 0.04
Pulmonary trunk (mm)	NA		21 ± 2.6	< 0.001	18 ± 2.2

[a] Differences between APE and APE follow-up.
[b] Differences between APE follow-up and controls .
Abbreviations: AcT = acceleration time of pulmonary ejection, APE = acute pulmonary embolism, NA = not available, RV = right ventricle, LV = left ventricle, TVPG = tricuspid valve peak systolic gradient, NS = not significant.

0.18). Doppler parameters showed elevated TVPG (48 ± 13 mmHg) and shortened AcT (58 ± 15 ms). Pharmacologic treatment and subsequent secondary prophylaxis of APE significantly reduced signs of RV overload (Table II). However, mean RV diameter and RV/LV ratio at follow-up were still increased when compared with controls (27 ± 2 vs. 23 ± 2 mm, $p < 0.001$, and 0.57 ± 0.1 vs. 0.49 ± 0.04, $p < 0.001$). Furthermore, the mean diameter of the pulmonary trunk was significantly larger in patients with APE at follow-up than in controls (21 ± 2.6 vs. 18 ± 2.2 mm, $p < 0.001$). Doppler assessment showed that AcT was markedly shorter in the whole APE group than in controls (97 ± 19 vs. 123 ± 19 ms, $p < 0.001$). The TVPG could be measured in 13 patients at follow-up and in 9 controls. Although the mean value of TVPG in the APE group at follow-up was similar to that in controls (24 ± 8 vs. 24 ± 8 mmHg, NS), elevated pulmonary systolic pressure (TVPG 32, 37, 38 mmHg, respectively) persisted in three patients with APE (8.3%), while TVPG > 30 mmHg (35 mmHg) was found in only one of the control subjects. Of interest, the Tei index was statistically significantly higher in APE in the follow-up group than in the control group (0.33 ± 0.06 vs. 0.30 ± 0.04, $p = 0.03$).

Six-Minute Walking Test

Results of the 6-MWT are shown in Table III. Although the mean 6-MWT distance tended to be shorter in APE than in controls at follow-up, the difference did not reach statistical

TABLE III Six-minute walking test parameters recorded in patients with acute pulmonary embolism at follow-up and in age- and sex-matched controls

Parameter	APE follow-up (n = 36)	Controls (n = 30)	p Value
Distance (m)	480 ± 141	527 ± 101	NS
SO^2 at rest (%)	95 ± 2	97 ± 1	0.003
SO^2 after test (%)	92 ± 2	95 ± 1	< 0.001
Desaturation after test (%)	3.04 ± 2.08	1.45 ± 0.69	0.0005
HR before test (1/s)	78 ± 11	69 ± 10	0.02
HR after test (1/s)	113 ± 17	104 ± 13	0.02

Abbreviations: APE = acute pulmonary embolism, HR = heart rate, SO^2 = saturation of capillary blood.

significance (480 ± 141 vs. 527 ± 101 m, NS). The mean saturation of capillary blood before and after the 6-MWT was statistically markedly lower in the APE follow-up group than in controls (95 ± 2 vs. 97 ± 1%, p = 0.003 and 92 ± 2 vs. 95 ± 1%, p < 0.001, respectively). It is interesting that mean desaturation after the 6-MWT was significantly more pronounced in the APE group than in controls (3.04 ± 2.08% vs. 1.45 ± 0.69%, p = 0.0005). Heart rate before and after the test was statistically significantly higher in the APE group than in controls (78 ± 11 vs. 69 ± 10 1/s, p = 0.02, and 113 ± 17 vs. 104 ± 13 1/s, p = 0.02).

In the APE group at follow-up, the 6-MWT distance related significantly positively with AcT (r = 0.58, p < 0.001) and negatively with TVPG (r = −0.67; p = 0.02, n = 13). However, a similar correlation was observed in controls (r = 0.60, p < 0.001; and r = −0.76, p = 0.02, n = 9, respectively). The subgroup of 6 patients with APE treated in the acute phase with thrombolysis was younger than 30 others who were only anticoagulated (57 ± 14 vs. 67 ± 10 years, p = 0.04). At diagnosis, among echocardiographic parameters, only the dimension of the inferior vena cava (23.0 ± 7.7 vs. 17.3 ± 4.8 mm, p = 0.02) and the Tei index (0.51 ± 0.14 vs. 0.37 ± 0.11, p = 0.02) were significantly different in these subgroups. No differences were found at follow-up between clinical, echo Doppler parameters and 6-MWT data between subgroups of patients with APE treated with thrombolysis and those who received anticoagulation alone, but this could be due to the low number of patients studied.

The same analysis of clinical, echocardiographic and 6-MWT parameters was performed in both groups after the exclusion of patients with elevated TVPG > 30 mmHg (three patients from the APE follow-up group and one patient from the control group). Also, there were no differences between clinical characteristics of patients with APE and controls at follow-up. Moreover, the same differences in echo-Doppler indices and in 6-MWT parameters persisted as observed in all groups of patients.

Discussion

The short-term clinical course of pharmacologically treated patients with APE has been extensively evaluated and indicates rapid resolution of signs of RV pressure overload. In the majority of survivors, thrombolysis as well as anticoagulation alone causes regression of clinical and echocardiographic symptoms of RV overload within 3–6 weeks.[4, 9] In addition, pulmonary angiographic studies revealed that in most cases of APE the resolution of thromboemboli occurred within 21 days.[5] However, it was reported that in some patients after APE, residual perfusion defects could be detected by control lung scintygraphy or spiral computer tomography even in spite of adequate long-term treatment.[10, 11] Moreover, recent studies have shown that in some patients with APE symptomatic pulmonary hypertension might persist or develop despite treatment. This evolution was reported more frequently in patients with more marked signs of RV overload found at the time of diagnosis of APE.[4]

Our study showed that even beyond 1 year of follow-up of APE, patients present echocardiographic and functional abnormalities when compared with age- and gender-matched controls. Although the majority of patients with APE were found to have normal systolic pulmonary arterial pressure as assessed by Doppler echocardiography, they had larger RV and a higher Tei index than age-matched controls. Recently, several studies observed elevated cardiac troponins especially in patients with RV overload, suggesting myocardial injury during the acute phase of APE.[12–14] Moreover, autopsy and scintigraphic case series reported RV MIs in patients with major APE.[15, 16] Therefore, larger RV dimension and higher Tei index found at follow-up in the APE group may result from damage-induced RV remodelling.

On the other hand, our data also showed differences in Doppler indices of RV pulmonary arterial coupling between the patients and the control group. Acceleration time of pulmonary ejection was significantly shorter in the former group, while the dimension of the pulmonary trunk was greater. These findings may suggest a persistently increased afterload in patients with APE despite antithrombotic treatment and secondary prophylaxis. Pulmonary hypertension after APE can be related to inadequate thrombolysis with subsequent clot remodelling or progressive changes in the pulmonary microvasculature.[17] Recurrent thromboembolic events or previous nondiagnosed and thus untreated episodes should also be considered. However, patients with proven or even suspected recurrence were not included in the present study, and in all cases the duration of symptoms suggestive of APE did not exceed 14 days before diagnosis. In three (8.3%) patients after APE, TVPG was > 30 mmHg indicating pulmonary hypertension. Previous studies suggested that approximately 0.5–1% of patients after APE can develop chronic thromboembolic pulmonary hypertension,[18, 19] but a recent trial suggested this prevalence to reach 5.1%.[4]

We used the 6-MWT to assess functional capacity of patients after APE. There were no significant differences in walking distance covered between both groups. However, patients after APE had a higher heart rate and lower blood saturation before and after the test. The 6-MWT causes significant desaturation in patients with APE. Of interest, in both groups walking distance correlated positively with acceleration of pulmonary ejection and was related negatively to TVPG.

Limitations of the Study

This study was partly retrospective with limitations characteristic of such trials. The main aim of the study was to assess the long-term consequences of pharmacologically treated APE on morphologic and functional indices described by echo Doppler and 6-MWT parameters. Therefore it was restricted to nonconsecutive patients who were assessed with echocardiography at the time of diagnosis and were found to have signs of RV overload before initiation of treatment. While we made all efforts to match our control and study groups carefully, this may also represent a source of bias. Furthermore, we

were not able to assess the clinical consequences of an apparently aborted resolution of changes induced by APE, admittedly resulting in relatively mild differences when compared with age-matched controls.

Conclusions

Standard and apparently successful treatment of acute pulmonary embolism does not prevent from mild persistent changes in morphology and function of the cardiovascular system. Despite normalization of pulmonary artery systolic pressure and similar exercise capacity, survivors of APE present signs suggesting RV dysfunction and/or its disturbed coupling to the pulmonary arterial bed as well as ventilation to perfusion mismatch at exertion persisting long after the acute embolic episode. The clinical significance of those long-term consequences of APE remains to be established.

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