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Multiple Beneficial Effects of Balloon Pulmonary Angioplasty in Patients With Chronic Thromboembolic Pulmonary Hypertension

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Background: Pulmonary arterial hypertension with systemic dysfunctions, including metabolic disorders and renal dysfunction, has a poor prognosis. However, it remains to be elucidated whether chronic thromboembolic pulmonary hypertension (CTEPH) is also associated with systemic dysfunctions, and if so, whether balloon pulmonary angioplasty (BPA) improves them.

Methods and Results: Fifty-five consecutive patients who underwent BPA from March 2012 to December 2014 for systemic dysfunctions, including glycemic control, lipid profiles, renal and vascular function, and nutritional status were examined. The analyses were performed before and after BPA (mean, 3.5 sessions/patient) and changes in hemodynamic parameters were compared. The average follow-up period was 474±245 days. Baseline prevalence of hypertension, diabetes mellitus, dyslipidemia and advanced chronic kidney disease was 58, 7, 33 and 36%, respectively. BPA caused marked hemodynamic improvements in the CTEPH patients. Importantly, BPA also significantly improved dysglycemia (fasting blood sugar, hemoglobin A1c and homeostatic assessment model of insulin resistance), renal (creatinine and estimated glomerular filtration rate) and vascular (cardio-ankle vascular index) functions and nutritional status (albumin, cholesterols, and body mass index). Importantly, there were positive correlations between the degrees of the hemodynamic improvements and those of other improvements.

Conclusions: These results indicate that BPA may exert multiple beneficial effects in CTEPH patients, not only in terms of hemodynamics but also in other systemic functions, with positive correlations among them. (*Circ J* 2016; **80:** 980–988)

Key Words: Balloon pulmonary angioplasty; Chronic thromboembolic pulmonary hypertension; Metabolic dysfunction; Pulmonary hemodynamics; Systemic dysfunction

Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by chronic and mechanical thromboembolic obstruction of large and small pulmonary arteries, with high mortality without intervention.[1,2] Although pulmonary endarterectomy (PEA) is recommended for the treatment of CTEPH, 37% of the cases are considered inoperable.[3] Recently, we and others have demonstrated that balloon pulmonary angioplasty (BPA) markedly improves the pulmonary hemodynamics and the long-term prognosis in CTEPH patients.[4–6]

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Several medical conditions have been reported to be involved in the development of CTEPH, including splenectomy, ventriculo-atrial shunt, inflammatory bowel disease and previous cancers.[1] These conditions increase the risk of a poor outcome in CTEPH patients. Systemic dysfunctions are also associated with pulmonary arterial hypertension (PAH) and PAH-associated death, including insulin resistance, dyslipidemia and renal

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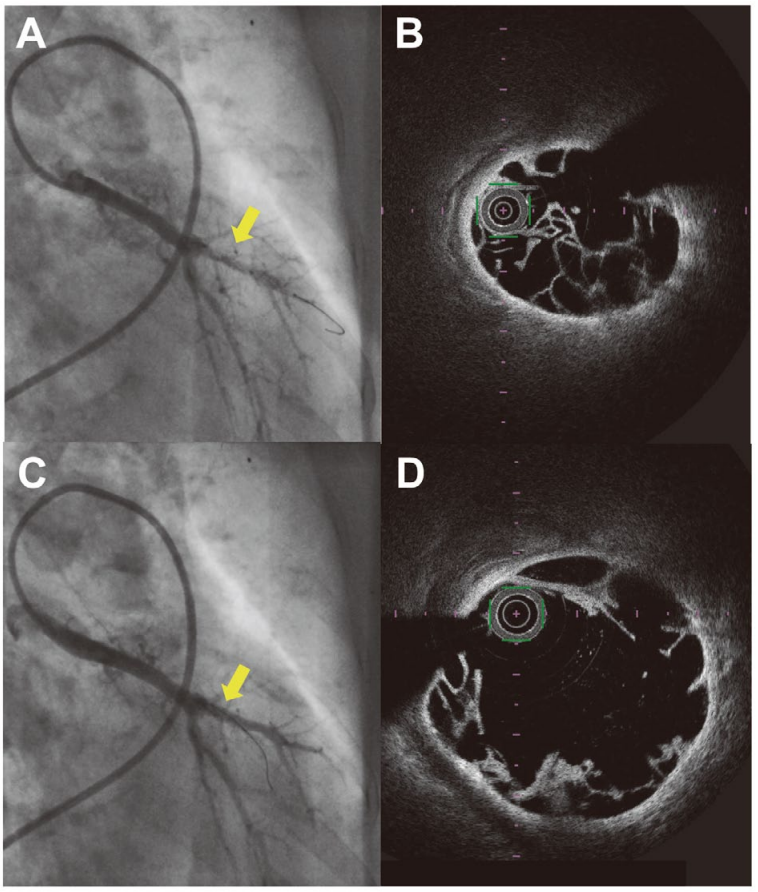

Figure 1. Angiographic and OFDI images of a representative case treated with balloon pulmonary angioplasty (BPA). (**A**,**C**) Pre-BPA angiogram. (**A**) The stenosis of a distal pulmonary artery (arrow), which was successfully treated by BPA (**C**). (**B**,**D**) By OFDI, elimination of the intravascular web can be clearly seen (**B**) before and (**D**) after BPA. OFDI, optical frequency domain imaging.

dysfunction.[7–9] The coexistence of metabolic dysfunction, anemia, arterial disease, hypertension, and cachexia is frequently observed in patients with chronic heart failure (CHF) and chronic kidney disease (CKD); this is known as the cardiorenal syndrome.[10] Because circulatory disturbances are common underlying features of PAH, CHF and CKD, we hypothesized that systemic dysfunctions are also associated with CTEPH and its hemodynamic severity.

In the present study, we thus examined whether CTEPH is associated with systemic dysfunctions in proportion to the severity of the disorder and, if so, whether BPA also improves the systemic dysfunctions along with hemodynamic improvements in CTEPH patients.

Methods

The present study was approved by the Ethics Committee of Tohoku University Graduate School of Medicine. Written informed consent was obtained from all patients.

Study Population

From January 1995 to December 2014, 110 patients with CTEPH were admitted to our hospital. BPA was instituted as the first-line therapy for inoperable CTEPH in mid-2009 in Tohoku University Hospital.[4] To examine the hypothesis that metabolic and renal dysfunctions are associated with CTEPH severity and BPA efficacy, we prospectively examined the clinical data of 55 patients who underwent BPA after March 2012. Twenty out of the 55 patients treated with anti-hyperglycemic or anti-hyperlipidemic drugs were excluded from the analysis for systemic dysfunctions because these drugs could influence the results of blood tests.

Diagnosis of CTEPH and Indication of BPA

CTEPH was diagnosed by a complete workup for pulmonary hypertension (PH),[11] including blood tests, chest X-ray, electrocardiogram, pulmonary function test, echocardiography, ventilation/perfusion lung scan, computed tomography,[12] right heart catheterization (RHC) and a traditional pulmonary angiography (**Figures 1A**,**C**).[13] In addition, we routinely performed pulmonary optical frequency domain imaging (OFDI) for accurate evaluation of the nature and extent of thromboembolic lesions in the small pulmonary arteries (**Figures 1B**,**D**).[14] Indication of BPA was judged for each patient by experienced cardiothoracic surgeons, cardiologists, and radiologists based on the thromboembolic lesions' locations, patient age, comorbidities and frailty.[4] A total of 55 patients were diagnosed as having symptomatic and inoperable CTEPH, and BPA was planned for them after informed consent was obtained.

BPA Procedures

Standard BPA procedures were previously described in detail.[4,5] Briefly, BPA was performed after anticoagulant administration for at least 6 months and stabilization of right heart failure with pulmonary vasodilators for 2 months when needed. After RHC with intravenous heparin, a selective

Table 1. Baseline Characteristics of Patients With Inoperable CTEPH

	All patients (n=55)	Patients without DM or dyslipidemia (n=35)	Patients with DM and dyslipidemia (n=20)
Age (years)	64±13	63±14	66±12
Female	42 (76)	26 (74)	16 (80)
BMI (kg/m^2)	23.6±3.9	23.3±3.4	24.2±4.8
WHO functional class			
I/II	0 (0)/33 (60)	0 (0)/22 (63)	0 (0)/11 (55)
III/IV	21 (38)/1(2)	12 (34)/1 (3)	9 (45)/0 (0)
Hypertension	32 (58)	19 (54)	13 (65)
Dyslipidemia	18 (33)	0 (0)	18 (90)**
DM	4 (7)	0 (0)	4 (20)*
Insulin resistance	30 (55)	21 (60)	9 (45)
Anemia	16 (29)	12 (34)	4 (20)
CKD ≥stage 3	20 (36)	13 (37)	7 (35)
Atrial fibrillation	1 (2)	1 (3)	0 (0)
Smoking			
History	18 (34)	14 (41)	4 (21)
None	35 (66)	20 (59)	15 (79)
BNP (pg/ml)	247±223	253±237	238±204
Mean session no. of BPA/patient	3.5±1.5	3.5±1.6	3.5±1.8
Follow-up period (days)	474±245	474±251	474±241
Epoprostenol	1 (2)	1 (3)	0 (0)
Oral prostanoids	28 (51)	16 (46)	12 (60)
PDE5i	36 (65)	23 (67)	13 (65)
ERA	9 (16)	7 (20)	2 (10)
Combination therapy	25 (45)	15 (43)	10 (50)
Diuretics	26 (47)	18 (51)	8 (40)
Warfarin	51 (93)	32 (91)	19 (95)
Oxygen therapy	41 (75)	27 (77)	14 (70)

Results are expressed as a number (%) or mean±SD. *P<0.05, **P<0.01 vs. patients without DM and dyslipidemia. BMI, body mass index; BNP, brain natriuretic peptide; BPA, balloon pulmonary angioplasty; CKD, chronic kidney disease; CTEPH, chronic thromboembolic pulmonary hypertension; DM, type 2 diabetes mellitus; ERA, endothelin receptor antagonists; PDE5i, phosphodiesterase-5 inhibitors; WHO, World Health Organization.

pulmonary angiography was performed to determine target lesions with intravascular webs, filling defects or complete occlusion. The selection of balloon size for BPA was based on the angiographic and OFDI-derived diameter of the target vessel (Figures 1A,B). The effectiveness and safety of BPA were also assessed by these 2 modalities after inflation (Figures 1C,D).[15] The BPA procedure was limited to a maximum of 2 lobes per procedure. The patients were monitored for possible reperfusion pulmonary edema for 1 day after BPA. BPA was repeated until the mean pulmonary arterial pressure (mPAP) was decreased below 30 mmHg.[5]

Hemodynamic Examination

RHC was repeated at baseline and at follow up. Hemodynamic parameters measured included mean right atrial pressure (mRAP), mPAP and mean pulmonary capillary wedge pressure (mPCWP). Pulmonary vascular resistance (PVR) was calculated from cardiac output (CO) using the Fick principle.

Data Collections

Baseline demographic data were collected from patient medical records (Table 1). Hypertension, dyslipidemia and diabetes mellitus (DM) were defined by prior diagnosis, known abnormal values or the use of drugs for each disorder. Anemia was defined by the World Health Organization (WHO) criteria.[16] CKD stage was determined by estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease formula modified for Japanese.[17]

Blood Analysis

Fasting venous blood samples were collected from patients before and after BPA. The average follow-up period was 474±245 days (interquartile range (IQR) 252–687) for all patients, 474±251 days (IQR 252–683) for the patients included and 474±241 days (IQR 229–716) for those excluded. Laboratory parameters measured included complete blood count, creatinine (Cr), uric acid (UA), thyroid function tests (thyroid stimulating hormone, free triiodethyronine and free thyroxine), total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), free fatty acid (FFA) fractions including arachidonic acid (AA), docosahexaenoic acid (DHA), dihomo-γ-linolenic acid (DHLA) and eicosapentaenoic acid (EPA), fasting blood sugar (FBS), immuno-reactive insulin (IRI), hemoglobin A1c (HbA1c), creatinine kinase muscle-brain fraction (CK-MB), troponin T, and high-sensitive C reactive protein (hs-CRP). Standard biochemical values were measured using a LABOSPECT 008 automatic analyzer (Hitachi High Technologies, Tokyo, Japan). LDL-C was measured by the direct method. IRI values were measured on a COBAS 8000 modular analyzer (Roche Diagnostics, Tokyo, Japan) using an

Table 2. Effects of BPA on Functional Class, Exercise Capacity, and Hemodynamics

	Before BPA (n=35)	After BPA (n=35)	P value
WHO functional class			<0.01
I/II	0/22	7/28	
III/IV	12/1	0/0	
6MWD (min)	408±181	482±146	<0.01
BNP (pg/ml)	252±237	34±23	<0.001
Pulmonary specific therapy*	26 (74)	26 (74)	NS
Oxygen therapy	27 (77)	20 (57)	<0.05
mPAP (mmHg)	35±9	24±6	<0.001
mRAP (mmHg)	6±3	5±4	NS
mPCWP (mmHg)	10±4	10±3	NS
mAoP (mmHg)	85±15	81±13	NS
HR (beat/min)	68±9	61±9	<0.001
CI ($L \cdot min^{-1} \cdot m^{-2}$)	2.6±0.6	2.7±0.6	NS
PVR ($dyne \cdot s \cdot cm^{-5}$)	482±223	255±80	<0.001

Results are expressed as a number (%) or mean±SD. CI, cardiac index; HR, heart rate; mAoP, mean aortic pressure; mPAP, mean pulmonary artery pressure; mPCWP, mean pulmonary capillary wedge pressure; mRAP, mean right atrial pressure; NS, not significant; PVR, pulmonary vascular resistance; 6MWD, 6-min walk distance. *The number of patients taking any pulmonary specific vasodilators such as oral prostanoids, PDE5i or ERA. Other abbreviations as in Table 1.

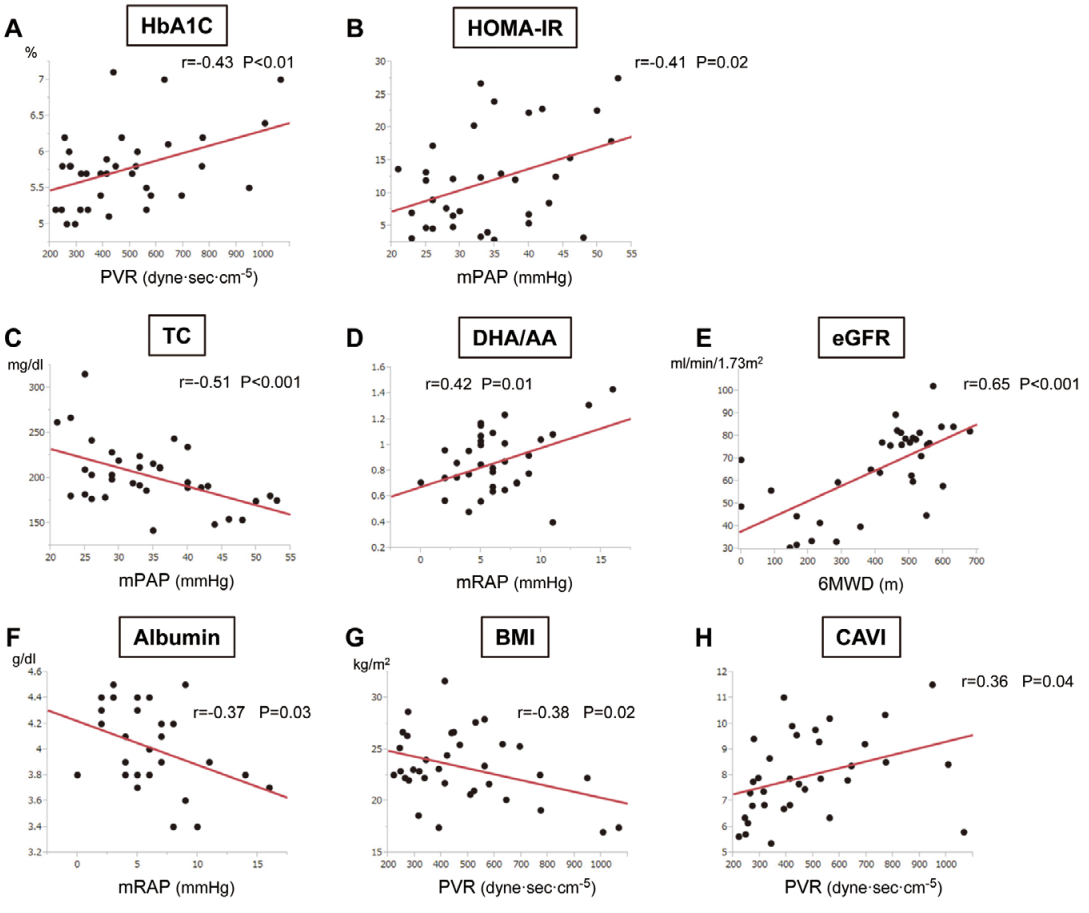

Figure 2. Correlation between hemodynamics and metabolic, renal and vascular functions. HbA1c, hemoglobin A1c; HOMA-IR, homeostasis model assessment of insulin resistance; TC, total cholesterol; DHA/AA, docosahexaenoic acid to arachidonic acid ratio; eGFR, estimated glomerular filtration rate; BMI, body mass index; CAVI, cardio-ankle vascular index.

Table 3. Effects of BPA on Glycemic Status and Lipid Profiles

	Before BPA (n=35)	After BPA (n=35)	P value
FBS (mg/dl)	98±13	92±11	<0.05
HbA1c (%)	5.8±0.5	5.6±0.4	<0.01
IRI (μU/ml)	11.9±7.3	8.0±4.9	<0.01
HOMA-IR	3.0±2.1	1.9±1.2	<0.01
TC (mg/dl)	202±36	214±38	<0.05
TG (mg/dl)	101±44	115±58	NS
LDL-C (mg/dl)	120±33	127±34	<0.05
HDL-C (mg/dl)	60±13	60±14	NS
LDL-C/HDL-C	2.1±0.8	2.2±0.8	NS
DHLA (μg/ml)	34.0±8.3	36.7±10.3	<0.05
AA (μg/ml)	183.1±39.8	193.5±40.6	NS
EPA (μg/ml)	73.7±34.4	94.7±41.3	<0.01
DHA (μg/ml)	152.5±35.9	169.3±40.1	<0.05
EPA/AA	0.42±0.18	0.52±0.28	<0.05
DHA/AA	0.86±0.24	0.91±0.29	NS
(EPA+DHA)/AA	1.28±0.40	1.43±0.54	NS

Results are expressed as a number (%) or mean±SD. AA, arachidonic acid; DHA, docosahexaenoic acid; DHA/AA, DHA to AA ratio; DHLA, dihomo-γ-linolenic acid; EPA, eicosapentaenoic acid; EPA/AA, EPA to AA ratio; (EPA+DHA)/AA, the sum of EPA and DHA to AA ratio; FBS, fasting blood sugar; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; IRI, immuno-reactive insulin; LDL-C, low-density lipoprotein cholesterol; LDL-C/HDL-C, LDL-C to HDL-C ratio; TC, total cholesterol; TG, triglyceride. Other abbreviations as in Tables 1,2.

electro-chemiluminescence immunoassay. FFAs were measured using a GC-2010 gas chromatograph (Shimadzu, Kyoto, Japan). Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the following formula: fasting IRI (μU/ml)×FBS (mg/dl)/405, with values above 2.0 indicating insulin resistance.[18] The urinary albumin-to-creatinine ratio (U-ACR) was also measured using first morning urine samples.

Assessment of Arterial Stiffness

For evaluating arterial stiffness, cardio-ankle vascular index (CAVI) was measured before and after BPA with a VaSera VS-1000 (Fukuda Denshi, Tokyo, Japan), as previously described.[19]

Statistical Analysis

Continuous variables are expressed as the mean±SD, and categorical variables as the number (%). Percent change in each clinical parameter before and after BPA was calculated as follows: percent change (Δ parameter)=[(post-BPA parameter)−(pre-BPA parameter)/pre-BPA parameter]×100. Means and percentages were compared using the Student's paired t-test, Wilcoxon signed-rank test, $\chi 2$ test or Fisher's exact test, as appropriate. Changes in WHO functional class and CKD stages over time were compared using the McNemar test. Linear regression analysis was used to evaluate the correlation between variables. P values of <0.05 were regarded to be statistically significant. All analyses were performed with JMP Pro 11.0.0 (SAS Institute Inc, Cary, NC, USA).

Results

Association Between CTEPH and Metabolic, Renal and Vascular Dysfunctions

Baseline characteristics of the 55 patients with inoperable CTEPH who underwent BPA and tests for systemic dysfunctions are shown in Table 1. Their mean age was 64 years old; females accounted for 76%, and more than half of them had hypertension and insulin resistance (Table 1). Dyslipidemia, anemia, advanced CKD and history of smoking were noted in approximately 30% of the patients. Clinical characteristics were similar between the patients included (n=35) and those excluded (n=20) for systemic dysfunctions analysis (Table 1).

Baseline pulmonary hemodynamics of the 35 inoperable CTEPH patients without DM or dyslipidemia are shown in Table 2. Regarding severity of PH, 37% of the patients had advanced WHO functional class, and their mean 6-min walk distance (6MWD) and serum level of brain natriuretic peptide (BNP) was 408 m and 252 pg/ml, respectively (Table 2). In pulmonary hemodynamics at baseline, mPAP and PVR were 35 mmHg and 482 dyne·s·cm^{-5}, respectively (Table 2).

The correlations between hemodynamic parameters and metabolic profiles at baseline are shown in Figure 2 and Table S1. The mPAP was significantly associated with HOMA-IR and TC, while PVR was significantly associated with HbA1c, body mass index (BMI) and CAVI (Figures 2A,C,G,H). The mRAP was significantly correlated with DHA/AA and albumin (Figures 2D,F). The highest correlation was noted between 6MWD and eGFR (Figure 2E).

Beneficial Effects of BPA on Hemodynamics and Metabolic, Renal and Vascular Dysfunctions

Changes in WHO functional class, exercise tolerance and hemodynamics after BPA are shown in Table 2. The mean number of BPA sessions was 3.5 per patient (range, 1–8). BPA significantly improved WHO functional class, 6MWD and BNP level, and reduced the need for oxygen therapy (Table 2). For hemodynamics, BPA significantly reduced mPAP, heart rate and PVR (Table 2).

Table 3 shows the effect of BPA on glycemic and lipid

Table 4. Effects of BPA on Renal, Vascular and Other Clinical Parameters

	Before BPA (n=35)	After BPA (n=35)	P value
Hb (g/dl)	13.1±2.1	12.7±1.5	NS
RDW (%)	13.9±1.5	13.5±1.0	<0.05
Lymphocytes (cells/μl)	1,425±550	1,609±571	<0.05
Reticulocytes (%)	1.37±0.58	1.43±0.42	NS
hTSH (μIU/ml)	2.84±3.91	2.89±3.50	NS
fT3 (pg/ml)	2.82±0.39	2.70±0.36	<0.05
fT4 (ng/ml)	1.25±0.18	1.22±0.16	NS
Albumin (g/dl)	4.0±0.3	4.1±0.3	NS
UA (mg/dl)	5.9±1.7	5.2±1.6	<0.01
Cr (mg/dl)	0.82±0.29	0.74±0.25	<0.001
eGFR (ml/min/1.73 m^2)	65.5±18.8	71.8±19.5	<0.001
CKD ≥stage 3	13 (37)	7 (20)	<0.05
U-ACR (mg/g·Cre)	36.4±50.4	29.3±78.2	NS
CK-MB (U/L)	11.4±3.6	9.8±3.8	<0.01
Troponin T (ng/ml)	0.012±0.011	0.010±0.010	NS
Ferritin (ng/ml)	69.8±60.6	59.8±52.2	NS
HS-CRP (mg/dl)	0.237±0.535	0.287±0.834	NS
BMI (kg/m^2)	23.3±3.4	24.1±2.8	<0.05
CAVI (m/s)	8.0±1.6	7.4±1.1	<0.01

Results are expressed as a number (%) or mean±SD. CAVI, cardio-ankle vascular index; CK-MB, creatine kinase muscle brain faraction; Cr, creatinine; eGFR, estimated glomerular filtration rate; fT3, Free Triiodethyronin; fT4, Free Thyroxine; Hb, hemoglobin; HS-CRP, high sensitive C-reactive protein; hTSH, human thyroid stimulating hormone; RDW, red blood cell distribution width; UA, and uric acid; U-ACR, urinary albumin to creatinine ratio. Other abbreviations as in Tables 1,2.

profiles. BPA significantly decreased FBS, HbA1c, serum insulin and HOMA-IR, and also significantly increased TC, LDL-C, DHLA, EPA, DHA and EPA/AA (Table 3).

Changes in renal, vascular, and other clinical parameters related to erythropoiesis, thyroid function, cardiac injury, inflammation and nutritional status after BPA are shown in Table 4. Regarding renal functions, there were significant decreases in serum Cr and UA, increased eGFR, and improvement in CKD stage after BPA. Marked decrease in CAVI values was also noted. Regarding nutritional status, BPA significantly improved total lymphocyte count and BMI. There were also significant decreases in red cell distribution width (RDW), free triiodothyronine (fT3) and CK-MB.

Figure 3 shows the correlations between percentage change in hemodynamic parameters and those in metabolic, renal and vascular functions after BPA. All correlation data can also be found in Table S2. The percentage change in 6MWD was significantly correlated with that in HbA1c (Figure 3A) and albumin (Figure 3K). There were significant correlations between the percent change in BNP and that in LDL-C, EPA, EPA/AA, and U-ACR (Figures 3F–I). Hemodynamic improvement in mRAP was also significantly correlated with that in HOMA-IR (Figure 3B), TC (Figure 3D) and U-ACR (Figure 3J). The percentage change in TC was also significantly correlated with that in mPAP (Figure 3C) and cardiac index (CI) (Figure 3E). Finally, the percentage change in CI was significantly correlated with that in total lymphocyte numbers (Figure 3L).

Discussion

The major findings of the present study were that: (1) systemic dysfunctions in the metabolic, renal, vascular and nutritional systems were common in inoperable CTEPH patients in proportion to the severity of the disorder; and (2) BPA ameliorated those dysfunctions along with marked hemodynamic improvements, with significant correlations among the improvements. To the best of our knowledge, this is the first report demonstrating the correlations between CTEPH and systemic dysfunctions and the marked effectiveness of BPA to improve such systemic dysfunctions as well.

BPA Strategy Has a Positive Impact on Inoperable CTEPH

Although PEA is the established treatment for CTEPH, 37% of patients are deemed inoperable[3] and approximately 25% have high PVR long after PEA.[20] Although specific pulmonary vasodilators are an alternative therapy,[21] medical treatment alone is not sufficient to ameliorate mechanical obstructions of the small pulmonary artery.[14] Thus, BPA is an emerging attractive strategy for inoperable CTEPH. BPA was first used for inoperable CTEPH in the 1990s,[22] and is now widely performed in Japan.[4–6,23] Indeed, BPA dramatically improves not only pulmonary hemodynamics but also functional status, exercise capacity and right ventricular functions,[5,22–24] which was also confirmed in the present study.

Clinical Characteristics of Patients With Inoperable CTEPH

It has been reported that development of CTEPH is associated with splenectomy, ventriculo-atrial shunt, inflammatory bowel disease and previous cancer.[1] Also, it has been recently reported that metabolic syndrome, insulin resistance and low HDL-C are associated with PAH.[7,9] Patients with pulmonary venous hypertension are frequently obese, hypertensive and diabetic.[25] Renal dysfunction was also associated with poor outcomes in PAH patients.[8] In the present study, a large proportion of CTEPH patients had the component of metabolic

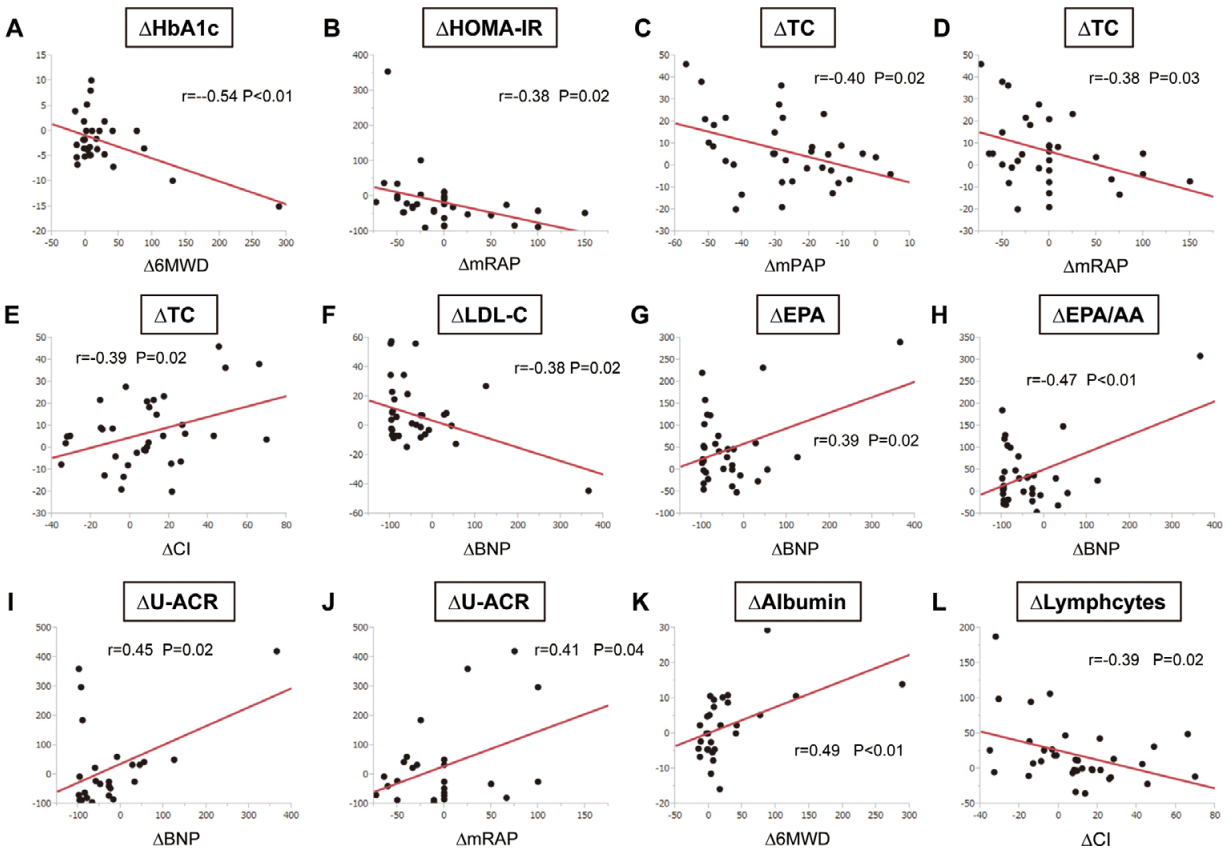

Figure 3. Correlation between percentage changes in hemodynamics and those in metabolic, renal and vascular functions after balloon pulmonary angioplasty (BPA). Δ indicates percentage change in each clinical parameter before and after BPA. HbA1c, hemoglobin A1c; HOMA-IR, homeostasis model assessment of insulin resistance; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; EPA, eicosapentaenoic acid; EPA/AA, EPA to arachidonic acid ratio; U-ACR, urinary albumin to creatinine ratio.

syndrome and advanced CKD. In the present study, the prevalence of pre-diabetes, defined as a HbA1c level of 6.0–6.4%, was 29% in female patients aged 60–69 years; this is more than two-fold higher than that of the general population (13%) in the Japan National Health and Nutrition Survey in 2013.[26] Similarly, in the present study, eGFR, TC and albumin levels were lower than in those women (65.5 vs. 74.9 ml/min/1.73 m^2, 202 vs. 220 mg/dl and 4.0 vs. 4.5 g/dl, respectively),[26] indicating that metabolic dysfunction and nutritional impairment are relatively common in CTEPH patients compared with that of the general population. However, compared with PAH patients, the prevalence of hypertension and dyslipidemia in our cohort were higher (58 vs. 54%, 33 vs. 17%, respectively), whereas that of diabetes was lower (7 vs. 20%).[25] This might imply that these conditions are associated with PH itself but not with a specific group of PH. It is important to note that these medical conditions were correlated with CTEPH severity. In the present study, impaired glucose metabolism, impaired renal function and enhanced arterial stiffness were all positively correlated with hemodynamic severity and exercise capacity, whereas nutritional parameters were negatively correlated with hemodynamic severity. PAH is more prevalent in women than in men,[27,28] which is also the case for non-operable CTEPH.[3] Female CTEPH patients are characterized by older age, more distal thrombi and a reduced improvement in PVR in response to PEA.[29] In the present study, the mean age of patients was >60 years and more than three-quarters were female, confirming the results of previous reports.[25–28]

Beneficial Effects of BPA on Systemic Dysfunctions

CHF is known to involve multiple organ systems, including neurohormonal activation, renal failure, obesity and metabolic dysfunctions encompassing dysglycemia, anemia, malnutrition and cachexia.[30] Although the pathophysiology of this relationship appears to be complex, hemodynamic impairment might play a major role in CHF-induced organ dysfunctions. Mechanical circulatory support devices, such as left ventricular assist device and intra-aortic balloon pump, improve end-organ dysfunction including dysglycemia in patients with advanced CHF.[31,32] We thus hypothesized that BPA could improve not only pulmonary hemodynamics but also systemic organ dysfunctions.

The present study demonstrates that CTEPH significantly improves WHO functional class, exercise capacity, and pulmonary hemodynamics in patients with inoperable CTEPH. Notably, BPA substantially improved systemic dysfunctions, including glycemic control (FBS, IRI, HbA1c and HOMA-IR), purine metabolism (UA), renal function (Cr and eGFR),

erythropoiesis (RDW), vascular stiffness (CAVI) and nutritional status (BMI, lymphocytes, albumin, TC, LDL-C and FFA). Furthermore, significant correlations were noted between improvements in hemodynamics and improvements in systemic dysfunctions systemic dysfunctions after BPA. BPA decreases right ventricular afterload by eliminating obstructions of small pulmonary arteries, leading to CI, mRAP and mPAP optimization. End-organ functional improvements could be achieved by increased organ perfusion and decreased organ venous congestion.[33] However, some improvements in systemic dysfunction were associated with improvements in functional and exercise parameters, but not with those in hemodynamics. Thus, improvements in heart failure symptoms after BPA may also be related with improvements in systemic dysfunctions.

Study Limitations

Several limitations should be mentioned for the present study. First, the present study was conducted in a single-center in a non-randomized fashion with a relatively low number of patients, which might explain why some variables of systemic dysfunction were associated with those of hemodynamic changes with a relatively low correlation coefficient. Second, systemic improvements could be achieved by pulmonary vasodilator treatment in cooperation with BPA therapy. A matched analysis between CTEPH and PAH patients is needed to assess the influence of these drugs. Third, we cannot deny the possibility that hospitalization itself improves systemic dysfunctions in CTEPH patients. However, in the present study, the patients underwent a mean of 3.5 BPAs during a mean of 4.7 hospitalizations per patient, and only one patient had both pre- and post-BPA examination during the first hospitalization. Thus, we consider that the improvements are directly related to the effect of BPA rather than that of hospitalization. Finally, because the data were assessed within a short-term period, it remains to be examined whether the beneficial effects of BPA on systemic dysfunction lasts for longer period of time.

Conclusions

In the present study, we were able to demonstrate that systemic dysfunctions are common in CTEPH patients, and that BPA might improve systemic dysfunctions associated with pulmonary hemodynamic improvements.

Acknowledgments

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Disclosures

The authors declare no conflicts of interest.

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Supplementary Files

Supplementary File 1

Table S1. Correlations between hemodynamics and parameters for systemic dysfunctions at baseline

Table S2. Correlations between percent changes in hemodynamics and those in parameters for systemic dysfunction after BPA

Please find supplementary file(s);
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