ONLINE SUPPLEMENTAL METHODS

Chronic thromboembolic pulmonary hypertension diagnosis and balloon pulmonary angioplasty procedure

Before the first balloon pulmonary angioplasty (BPA) session, patients were diagnosed with chronic thromboembolic pulmonary hypertension (CTEPH) using standard criteria and were considered inoperable, as previously described, which was confirmed by the multidisciplinary CTEPH team including radiologists and surgeons with expertise in pulmonary endarterectomy at our experienced pulmonary hypertension centre.[1, 2] All BPA procedures, consisting of a mean 4.2±1.8 (range, 2–8) sessions per patient between February 2011 and February 2015, were successfully performed as previously described, without any deaths or major complications, such as severe reperfusion pulmonary oedema.[1, 2] Each BPA session was repeated at an interval of at least one week. Of the total 803 BPA procedures, 346 were performed on segmental arteries and 457 on subsegmental arteries.

Outcome measures

Briefly, after a 2-min rest followed by a 1-min warm-up (0 W), cardiopulmonary exercise testing (CPX) was performed on an upright bicycle ergometer in a ramp pattern with a 10 or 15 W/min increment, as appropriate, to the symptom-limited maximum effort, as previously described.[2-4] Oxygen uptake (VO_2), carbon dioxide production (VCO_2), and minute ventilation (VE) were measured using breath-by-breath gas analysis. Peak VO_2 was determined as the higher value of either the greatest VO_2 during exercise or the average VO_2 in the final 18 s of exercise and was adjusted for age, sex, and body weight to derive percent-predicted peak VO_2 (%). Respiratory exchange ratio, exercise duration, peak work load (WR), delta VO_2/delta WR, resting and peak heart rates (HR), peak systolic and diastolic

blood pressure, recovery half-time of VO_2, and lowest pulse oximeter oxygen saturation (SpO_2) during exercise were also determined. The oxygen pulse was calculated by dividing VO_2 by HR. The VE-VCO_2 slope, an index of ventilatory efficiency during exercise, was determined using linear regression analysis of VE and VCO_2 from the beginning of exercise until the respiratory compensation point. The anaerobic threshold was determined using the V-slope method.[5] Maximal handgrip strength, as an index for forearm muscle strength, and maximal quadriceps isometric strength were measured using a hydraulic hand dynamometer (North Coast™, North Coast Medical, CA, USA) and a hand-held dynamometer (μ Tas F-1, ANIMA, Tokyo, Japan), respectively.

Right heart catheterisation was performed just before removal of the Swan-Ganz catheter on the day after the final BPA and at the 3-month follow up, to measure mean pulmonary artery wedge pressure (PAWP), mean pulmonary arterial pressure, mean right atrial pressure, cardiac output, pulmonary vascular resistance (PVR), and total pulmonary resistance, as previously described.[1, 2] The latter procedure was performed with pulmonary digital subtraction angiography to confirm the results of BPA. On the day after the final BPA, we were unable to obtain PAWP and subsequent PVR. Health-related quality of life scores and depressive symptoms were assessed with the Short Form Health Survey and Patient Health Questionnaire-9, respectively.

Exercise training programme

HR and SpO_2 were continuously monitored. The target exercise intensity was determined individually based on 40–60% of HR reserve (Karvonen's equation, k=0.4–0.6)[6, 7] obtained by symptom-limited CPX or at the 12–13 level of the 6–20 Borg scale of perceived exercise effort.[7, 8] Patients were instructed to maintain SpO_2 ≥90% during exercise and decrease their pace when SpO_2 fell below 90%. Patients receiving oxygen therapy before inclusion

continued the supplemental oxygen. Home exercise consisted of walking at a prescribed HR for 30–60 minutes 4–5 times/week and low-intensity resistance training of the lower limbs 3 days/week, while monitoring SpO_2. In addition to exercise training, patients received patient education, lifestyle guidance, counselling, and psychological support by the multidisciplinary team throughout the study period. All patients, including the non-cardiac rehabilitation group, were asked to record the time (/day) and frequency (/week) of home exercise.

ONLINE SUPPLEMENTAL RESULTS

Non-responders

One of the two non-responders already had excellent exercise capacity (percent-predicted peak VO_2 of 90.1%) at baseline, likely contributing to the slight decrease in peak VO_2 (–1.6%), whereas the worst reduction (–11.6%) was associated with the least frequency of home exercise (1.0 day/week), likely due to a concurrent mental disorder.

REFERENCES

1 Fukui S, Ogo T, Morita Y, et al. Right ventricular reverse remodelling after balloon pulmonary angioplasty. *Eur Respir J* 2014;43:1394–402.

2 Fukui S, Ogo T, Goto Y, et al. Exercise intolerance and ventilatory inefficiency improve early after balloon pulmonary angioplasty in patients with inoperable chronic thromboembolic pulmonary hypertension. *Int J Cardiol* 2015;180:66–8.

3 Balady GJ, Arena R, Sietsema K, et al. Clinician's Guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. *Circulation* 2010;122:191–225.

4 Iwase T, Nagaya N, Ando M, et al. Acute and chronic effects of surgical thromboendarterectomy on exercise capacity and ventilatory efficiency in patients with chronic thromboembolic pulmonary hypertension. *Heart* 2001;86:188–92.

5 Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol* 1986;60:2020–7.

6 Karvonen MJ, Kentala E, Mustala O. The effects of training on heart rate; a longitudinal study. *Ann Med Exp Biol Fenn* 1957;35:307–15.

7 Suzuki S, Takaki H, Yasumura Y, et al. Assessment of quality of life with 5 different scales in patients participating in comprehensive cardiac rehabilitation after acute myocardial infarction. *Circ J* 2005;69:1527–34.

8 Borg G. Perceived exertion as an indicator of somatic stress. *Scand J Rehabil Med* 1970;2:92–8.