

Mineralocorticoid receptor blockade improves pulmonary hypertension and right ventricular function in bronchopulmonary dysplasia: a case report

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Abstract: Bronchopulmonary dysplasia (BPD) is a combined pulmonary vascular and parenchymal disease, representing the most common cause of chronic lung disease (CLD) in infancy. Pulmonary hypertension (PH) is frequently associated with BPD and—if persistent—substantially increases mortality. We report on a 4-month-old, former preterm infant with BPD, severe PH and right heart failure who greatly and rapidly improved clinical status and right ventricular (RV) function by means of blood biomarkers [N-terminal prohormone of brain natriuretic peptide (NT-pro-BNP), cardiac troponin T] and transthoracic echocardiography, following the addition of spironolactone and hydrochlorothiazide to the treatment regimen.

Keywords: Pulmonary hypertension (PH); bronchopulmonary dysplasia (BPD); spironolactone; hydrochlorothiazide (HCTZ); case report

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Introduction

Bronchopulmonary dysplasia (BPD) is a combined pulmonary vascular and parenchymal lung disease representing the most common cause of chronic lung disease (CLD) in infancy (1,2). For almost two decades BPD has been defined as the need for supplemental oxygen use either at a corrected age of 36 gestational weeks (p.m.) or after 28 days of life (3), and the severity of BPD (mild, moderate or severe) has been determined at 36 weeks post-menstrual age (PMA) (3). However, in 2019, a new definition of BPD was proposed that includes infants on any form of respiratory support (such as high-flow nasal cannula) at 36 corrected weeks (p.m.), even in the absence of any supplemental oxygen administration (4). Regardless of which BPD definition may be used, pulmonary hypertension (PH)/pulmonary hypertensive vascular disease (PHVD) might be evident even before the formal diagnosis of BPD can be made (5), and is-importantly-a major determinant of clinical outcome in BPD: approximately

25% of infants with moderate to severe BPD develop PH (6,7) that affects heart and lungs, thereby greatly increasing mortality (i.e., 47% of BPD-infants die 2 years after diagnosis of PH) (8-10).

We present the following case in accordance with the CARE Guideline (available at http://dx.doi.org/10.21037/ cdt.2020.02.05).

Case presentation

A male, preterm infant [28 2/7 PMA; birth weight 600 g] presented postnatally with respiratory distress syndrome (RDS). On the second day of postnatal life the infant suffered from acute pulmonary hemorrhage so that the infant was transitioned from conventional to high frequency oscillatory ventilation (HFOV). Echocardiogram at this point showed adequate systolic function of the right ventricle (RV), but the degree of PH was estimated to be nearly systemic arterial pressure, based on the full flattening



Figure 1 Time course of serum NT-pro-BNP and cardiac troponin T (cTNT) during the 4-week treatment (day 1-28). Former preterm infant with bronchopulmonary dysplasia (BPD) showed at the age of 44 weeks p.m. significant tachydyspnea despite oxygen supplementation through nasal cannula, severe pulmonary hypertension and right heart failure. The highly elevated blood biomarkers NT-pro-BNP (11,702 ng/L) and cTNT (90 ng/L) indicated heart failure and moderate myocardial ischemia (reference level: NT-pro-BNP: ≤84 ng/L; cTNT: ≤14 ng/L). Treatment with spironolactone and hydrochlorothiazide (HTCZ) started at day 1. After seven days, serum NT-pro-BNP decreased by 94% (11,702 to 728 ng/L) and clinical conditions improved (infant's tachydyspnea disappeared). At day 28, serum NT-pro-BNP and HTC declined even further to -98% (11,702 to 192 ng/L) and -34% (90 to 59 ng/L) vs. day 1 of add-on treatment. After 3 months (day 101) of spironolactone/HCTZ treatment NTpro-BNP (124 ng/L) and cTNT (24 ng/L) have declined further. Follow-up data after nine months (day 276) showed sustained normal (low) serum NT-pro-BNP (129 ng/L) and further decrease of serum cTNT to the normal reference range (<10 ng/L). NTpro-BNP, N-terminal prohormone of brain natriuretic peptide.

of the interventricular septum in end systole, in the absence of tricuspid regurgitation (TR). In total, the infant underwent 12 postnatal days on mechanical ventilation, 40 days on continuous positive airway pressure (CPAP), 130 in hospital days, and 127 days on supplemental oxygen.

Four months later, at 44 gestational + postnatal weeks p.m. (body weight 2,600 g), the patient was spontaneously breathing on 1 L/min supplemental oxygen via nasal cannula, had significant tachypnea and dyspnea, negative viral panel, and patchy hyperdensities on chest X-ray, consistent with BPD. Laboratory findings of elevated NTpro-BNP (11,702 ng/L) and cardiac troponin T (cTNT; 90 ng/L; reference values: NT-pro-BNP: ≤84 ng/L; cTNT: \leq 14 ng/L; *Figure 1*) indicated heart failure and moderate myocardial ischemia. Echocardiographically, RV systolic pressure (RVSP) was estimated to be systemic or even slightly supra-systemic, using the CW Doppler velocity of the TR jet (4.1 m/s) and the simplified Bernoulli equation (*Figure 2A*). The RV was dilated and hypertrophied (*Figure 2B*) and longitudinal systolic RV function as judged by tricuspid annular peak systolic excursion (TAPSE), was moderately decreased (TAPSE 0.61 cm; reference values: 0.68–1.15 cm for term infants 0–30 days). There was mild TR (I°). Systolic left ventricular (LV) function and renal function were normal.

Treatment and outcome

To decrease pulmonary artery pressure and improve RV function, we initiated combined treatment with the mineralocorticoid receptor (MR) blocker spironolactone and hydrochlorothiazide (HCTZ; both 2×3 mg p.o.). After 7 days, the infant's tachypnea and dyspnea disappeared and general clinical condition had greatly improved, so that the patient was discharged from the hospital on supplemental oxygen (0.1 L/min, SpO₂ \geq 93%) 12 days after spironolactone/HCTZ had been started.

Intriguingly, NT-pro-BNP and cTNT decreased substantially within the first 1-4 weeks of MR blockade with spironolactone (Figure 1). Consistent with the laboratory findings, echocardiography 4 weeks after the start of MR blockade confirmed much improved PH and decreased RV dilation: TR was trivial and RVSP was measured to be less than half-systemic. The right ventricular internal diameter in diastole (RVIDD) decreased from 1.21 to 1.05 cm. RV/ LV systolic function and diameter were normal (Figure 2C). Because of these rapid improvements, a planned cardiac catheterization was cancelled and no additional "PH specific" therapy (e.g., sildenafil, bosentan) was initiated so far (5). Three months after start of spironolactone and HCTZ the patient had been weaned off oxygen, had less than half-systemic RV systolic pressure, decreased RVIDD (0.86 cm), decreased serum NT-pro-BNP (124 ng/L), and cTNT (24 ng/L) and normal longitudinal systolic RV function [TAPSE 1.1 cm; reference values 0.85-1.42 cm for term infants 1-3 months old (11)] (Figure 1,2D). After 9 months of MR blockade at a follow-up visit, that patient had constantly low (normal) serum NT-pro-BNP (129 ng/L) and serum cTNT that was further decreased into the normal reference range (<10 ng/L) (Figure 1). In accordance with these laboratory and imaging findings, tachydyspnea

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Figure 2 Transthoracic echocardiograms of a former preterm infant with bronchopulmonary dysplasia (BPD) and severe pulmonary hypertension and right heart failure (44–66 gestational + postnatal weeks p.m.). (A) Transthoracic echocardiography, parasternal short axis (44 gestational + postnatal weeks p.m., day 1 of spironolactone/HCTZ treatment): RV pressure is estimated to be systemic or even slightly supra-systemic, using the CW Doppler velocity of the TR jet (4.1 m/s) and the simplified Bernoulli equation. (B) Transthoracic echocardiography, parasternal short axis (44 gestational + postnatal weeks p.m., day 1 of spironolactone/HCTZ treatment): severe pulmonary hypertension (PH) with systemic-to slightly supra-systemic pressure in the right ventricle (RV). RV is dilated and hypertrophied, the interventricular septum is flattened at the end of systole. Systolic RV function was moderately decreased, systolic left ventricular (LV) function normal. (C) Transthoracic echocardiography, parasternal short axis (48 gestational + postnatal weeks p.m., day 28 of spironolactone/HCTZ treatment): improvement of PH decreased RV dilatation [interventricular septum is round bowing from left to right at the end of systole; right ventricular internal diameter in diastole (RVIDD): 1.21 to 1.05 cm]. RV and LV systolic function were found to be normal. (D) Transthoracic echocardiography, parasternal short axis (66 gestational + postnatal weeks p.m., day 101 of spironolactone/HCTZ treatment): the interventricular septal curvature indicates less than half-systemic RV systolic pressure, RV size has decreased (RVIDD 0.86 cm) and longitudinal systolic RV function (TAPSE 1.1 cm) was normal. TR, tricuspid regurgitation; HCTZ, hydrochlorothiazide; TAPSE, tricuspid annular peak systolic excursion.

and intermittent cyanosis disappeared within the first week of spironolactone/HCTZ treatment.

Discussion

BPD and associated PH/RV dysfunction in the first year of life are life-threatening conditions awaiting innovative diagnostic biomarkers such as galectin-3 (12), and effective treatment strategies, including MR blocking agents (13-16) and cell-based therapies that have the potential to reverse the underlying CLD (17-20).

We cannot fully rule out a synergistic effect of HCTZ

on MR blockade with spironolactone in this patient. However, the effect of the add-on medication on PH, biomarkers, and clinical status was rapid (within days) while the diuretic effect of both HCTZ and spironolactone is known to be mild and slow. Thus, we suggest MR blockade with spironolactone could be an adjuvant treatment for PH and RV dilation/dysfunction in infants. Clinically, both eplerenone and spironolactone are frequently used in patients with ventricular hypertrophy/remodeling and in those with RV and/or LV diastolic dysfunction [precapillary PH/pulmonary arterial hypertension (PAH), or heart failure with preserved ejection fraction (HFpEF) with or without postcapillary PH].

In a meta-analysis of nine HFpEF trials MR antagonist treatment significantly improved indices of cardiac structure and function, suggesting a decrease in LV filling pressure and reverse cardiac remodeling (21). The current NIH-sponsored "Pilot Study of Effect of Spironolactone Therapy on Exercise Capacity and Endothelial Dysfunction in Pulmonary Arterial Hypertension" (NCT0171262) aims to enroll 70 adult group 1 patients to either spironolactone (25–50 mg) or placebo. Patients with idiopathic PAH (IPAH) and disease-associated PAH will be recruited and enrolled in a randomized, double blinded, placebo-controlled study of early treatment with spironolactone to investigate its effects on exercise capacity, clinical worsening, and vascular inflammation *in vivo*.

Taken together, preterm infants with BPD and persistent, more than mild PH (>1/2 systemic RV pressure), and those with "out of proportion PH" (mild BPD/CLD but severe PH), should strongly be considered for early, full diagnostic work-up (including cardiac catheterization and subsequent "PH-targeted" pharmacotherapy (e.g., sildenafil +/- endothelin receptor antagonist) (5). Treatment efficacy of spironolactone and HCTZ in preterm BPD infants with right ventricular hypertrophy (RVH) and PH should be interpreted with caution as the current number of the published observations (including our case) is small, and more specific, prospective pediatric and adult PH studies on the efficacy of (add-on) MR blockade are warranted. Nevertheless, the 2019 Updated Guidelines of the European Pediatric Pulmonary Vascular Disease Network (EPPVDN) in this respect recommend "In infants with severe BPD with or without PH, judicious fluid management is important, and may include treatment with diuretics (i.e., HCTZ and spironolactone), as long as cardiac pre-load is adequate" (class of recommendation IA, level of evidence B) (5).

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Footnote

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