Urinary bicarbonate and metabolic alkalosis during exacerbations in cystic fibrosis

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To the Editor:

Pseudo-Bartter syndrome (PBS) is characterised by hypokalaemic, hyponatraemic and hypochloraemic metabolic alkalosis in the absence of renal tubules pathology; it is a well-recognised complication of cystic fibrosis (CF), in the context of dehydration and acute illness [1–7].

PBS occurs more frequently in children with CF, although it has been described in adults as well. Several studies have observed an increased prevalence of metabolic alkalosis in adults with CF, both during acute exacerbations and clinical stability [4, 6, 7], with metabolic alkalosis also being considered a contributing factor to hypercapnic respiratory failure [7].

Metabolic alkalosis in CF may be influenced directly by defective function of the CF transmembrane conductance regulator (CFTR) in the kidneys. CFTR is in fact widely expressed in the renal tubular system, where it regulates ion transport *via* interaction with other ion channels and pendrin [8, 9]. In CF, pendrin upregulation and function appears to be defective, leading to impaired secretion of bicarbonate (HCO_3^-) in the distal tubules [10, 11].

In this study, we explore acid-base disturbances, as well as urinary excretion of HCO_3^- and other electrolytes during acute pulmonary exacerbations in adults with CF.

A pilot feasibility study was completed, which included patients with CF admitted to hospital with an acute pulmonary exacerbation (defined according to the Fuchs' criteria); a control group with non-CF respiratory disease were recruited consecutively. Exclusion criteria were: treatment with diuretics, uncontrolled diabetes, >55 years of age and inability to provide consent. Outcomes of interest were: the feasibility of larger trials, the distribution of acid-base disturbances, and urinary excretion of HCO_3^- and other electrolytes in the studied cohorts.

Electronic medical notes (recorded using EMISweb (EMIS Health, Rawdon, UK) and PPM+ (PPM Software, Burton upon Trent, UK) were reviewed for collection of demographic, comorbidity, treatment and lung function data. Feasibility data (recruitment rate, data completion rate) were collected.

Arterial and/or arterialised capillary blood gases and urine samples for urinary electrolytes and HCO_3^- were taken simultaneously on admission. Blood gases were analysed according to the Stinebaugh–Austin diagram.

Spot urine samples for pH, HCO_3^- and chloride were collected in vacuum tubes and hand-delivered to the laboratory for immediate analysis, as previously described [12]. Fractional excretion was computed for the urinary electrolytes.

The study was approved by the Research Ethics Committee and Health Research Authority (14/NE/1197). Written, informed consent was obtained from all participants.

No sample size calculation was performed for this pilot study. We aimed to enrol 15 participants in each arm over a 3-month period.

Shareable abstract (@ERSpublications)
The aetiology of increased serum bicarbonate and metabolic alkalosis in CF is complex and appears to be driven, at least in part, by renal tubular CFTR dysfunction https://bit.ly/3NFPkUu

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Data distribution was assessed with normality tests (Shapiro–Wilk) and by visual inspection. Results are expressed as number (percentage), median (interquartile range) if non-normal distribution and mean±SD if normal distribution. A unpaired t-test and the Mann–Whitney U-test were used to compare each variable in the two arms (CF and controls); Pearson correlation was performed as appropriate. The Chi-squared test was used to assess differences in frequency distributions between groups. A p-value of <0.05 was considered statistically significant. All analyses were performed using IBM SPSS v26 (IBM corp, Armonk, NY, USA).

A total of 31 participants were enrolled in the study over a 6-month period: 15 in the CF arm and 16 in the control group. The recruitment rate was 3.75 subjects per month and differed in the CF cohort (3 subjects per month) compared with the non-CF cohort (5 subjects per month). There were no dropouts from the

TABLE 1 Baseline characteristics, and serum and urinary electrolyte data from the two cohorts

	Cases	Controls	p-value
Subjects, n	15	16	
Age, years	31 (26–35)	45 (33–59)	0.002
Males	10 (66.7)	7 (43.8)	0.2
BMI, kg·m^{-2}	22.5 (17.4–24.9)	27.8 (23–32)	0.007
FEV_1 %	36 (27–45)	61 (55–99)	<0.001
Emergency hospital admission	0	13 (81.3)	<0.001
Diagnosis			<0.01
CF	15 (100)		
F/F	9 (60)		
F/MF	3 (20)		
F/RF	3 (20)		
Asthma		9 (56.25)	
Non-CF bronchiectasis		3 (18.75)	
Pneumonia		3 (18.75)	
ILD		1 (6.25)	
Comorbidities			
Cardiovascular	1 (6.7)	5 (31.3)	0.083
Liver disease	10 (66.7)	1 (6.3)	0.002
Diabetes	4 (26.7)	1 (6.3)	0.061
ABG			
pH	7.46 (7.41–7.49)	7.43 (7.42–7.49)	0.953
P_{aCO_2} mmHg[#]	5.25 (4.88–5.73)	4.49 (4.26-4.68)	<0.001
P_{aO_2}, mmHg	9.6 (9–10.2)	11.29 (8.19–13.87)	0.281
HCO_3^-, mmol·L^{-1}	27.8 (26.3–30)	23.4 (22.9–24.5)	<0.001
BE, mmol·L^{-1}	3 (2–7)	−0.85 (−2.75–0.17)	<0.001
Serum HCO_3^-, mmol·L^{-1}	28 (25.5–28.5)	24 (22.5–24)	0.001
Serum chloride, mmol·L^{-1}	101 (97.5–104)	105 (102.5–106.5)	0.067
Serum sodium, mmol·L^{-1}	138 (137.5–140.5)	141 (138.5–141.5)	0.108
Serum potassium, mmol·L^{-1}	4.1 (3.9–4.3)	4.0 (3.8–4.2)	0.892
Urea, mmol·L^{-1}	4.2 (3.2–6.4)	5.5 (3.25–5.6)	1.0
Creatinine, µmol·L^{-1}	61 (45.5–91)	58 (53–64)	0.650
Urinary pH (lab)	6.0 (5.75–6.5)	6.0 (5.25–6.87)	0.918
Urinary HCO_3^-, mmol·L^{-1}	3.5 (1.22–5)	2.5 (0–9.75)	0.982
Urinary chloride, mmol·L^{-1}	133 (65.25–174.75)	49.5 (37.5–117)	0.070
Urinary sodium, mmol·L^{-1}	99 (65.75–157.75)	51.5 (29–91)	0.056
Urinary creatinine, mmol·L^{-1}	11 (5.27–12.25)	10.7 (4.72–16.96)	0.711
Fractional excretion			
Chloride, %	0.65 (0.42–1.05)	0.73 (0.21–1.08)	0.713
HCO_3^-, %	0.094 (0.04–0.29)	0.076 (0–1.08)	0.974
Sodium, %	0.54 (0.33–0.7)	0.57 (0.089–0.75)	0.533

Data are presented as n (%) and median (interquartile range), unless otherwise stated. BMI: body mass index; FEV_1: forced expiratory volume in 1 s; CF: cystic fibrosis; F/F: homozygous for the *F508del-CFTR* mutation; F/MF: heterozygous for the *F508del-CFTR* mutation and a minimal function *CFTR* mutation; F/RF: heterozygous for the *F508del-CFTR* mutation and a residual function *CFTR* mutation; ILD: interstitial lung disease; ABG: arterial blood gas; P_{aCO_2}: arterial carbon dioxide tension; P_{aO_2}: arterial oxygen tension; HCO_3^-: bicarbonate; BE: base excess. [#]: data presented as median (25th–75th percentile).

study and the data completion rate was 100%. The demographics and baseline characteristics of the two groups are presented in the table 1.

None of the participants received treatment with diuretics, acetazolamide or CFTR modulators. 11 subjects in each cohort were being treated with long-acting β-agonists (73.3% *versus* 68.75%; p=nonsignificant). 10 (62.5%) subjects in the control group and five (33.3%) subjects in the case cohort received treatment with a salbutamol nebuliser or inhaler (p<0.01). More participants in the control group received systemic steroids (81.25% *versus* 20%). All subjects in the CF cohort received treatment with intravenous antibiotics, whereas only nine subjects in the control group received antibiotics.

Baseline blood gas measurements were performed at room air in 13 (86.7%) subjects with CF and nine (56.7%) controls. All other blood gases were performed on supplemental oxygen, delivered *via* either nasal cannula or Venturi mask (table 1). There was no significant difference in arterial oxygen tension between the groups (mean difference −1.62 (95% CI −4.13–0.88)). Arterial carbon dioxide tension (P_{aCO_2}) and HCO_3^- were significantly higher in the CF cohort (mean difference in P_{aCO_2} 1.25 (95% CI 0.47–1.95) and mean difference in HCO_3^- 5.33 (95% CI 3.55–7.11)) (table 1), as was the frequency of metabolic alkalosis (46.7% *versus* 7.1%; p<0.01). In the control group, most blood gases were normal and respiratory alkalosis was the most frequent acid-base disturbance (25% of subjects). No cases of metabolic acidosis were seen in either group.

Serum HCO_3^- concentrations were higher in subjects with CF compared with controls (CF 28 (25.5–28.5) *versus* control 24 (23–24.75) mEq L^{-1}; p=0.004), irrespective of acid-base status. All serum electrolytes were within normal limits (table 1). No correlation was observed between the concentration of serum HCO_3^- and any of the other serum electrolytes, either in the overall population or within the separate cohorts.

No differences were observed in renal excretion of HCO_3^-, as shown by the similar urinary concentration and fractional excretion of HCO_3^-. There was no correlation between serum HCO_3^- concentration and urinary excretion of HCO_3^- in either the separate cohorts or the overall group (Pearson coefficient 0.077, p=0.833 for CF, and 0.046, p=0.899 for controls). A trend towards a higher urinary concentration of chloride and sodium was observed among subjects with CF, but fractional excretion was similar (table 1).

The aetiology of metabolic alkalosis in adults with CF is poorly understood [4, 6, 7]. In this small cohort, elevated serum concentrations of HCO_3^- appeared to occur frequently and were not associated with PBS. While metabolic alkalosis was the most frequent acid-base disturbance in this cohort of people with CF, raised HCO_3^- concentration was also observed in the context of normal acid-base balance. Despite normal serum electrolytes, the urinary concentration of sodium and chloride appeared to be higher in those with CF compared with controls, although the difference was not statistically significant (table 1). In contrast, there was no elevation in urinary HCO_3^- concentration, despite elevated serum levels.

As none of the participants received treatment with diuretics or acetazolamide, and antibiotics were commenced after blood gas and urine sampling, assessing urine chloride concentration within a clinical setting may help elucidate the aetiology of metabolic alkalosis. Traditionally, metabolic alkalosis with a low urinary chloride concentration (<20 mmol·L^{-1}) is associated with a post-hypercapnic status and/or diseases linked to chloride loss (including CF), whilst an elevation in sodium and chloride urinary levels usually reflects mineralocorticoid excess or disorders mimicking it, including primary activation of epithelial sodium channel [13].

While the similar fractional excretion of electrolytes with increased urinary concentration of chloride could reflect a more concentrated urine in response to dehydration, a known common feature of CF, the normal serum electrolytes and renal function in our cohort of people with CF suggest that dehydration is unlikely to be the primary mechanism involved.

People with CF can experience a transient increase in P_{aCO_2} during exercise and sleep [14]. Therefore, it could be hypothesised that the increase in serum HCO_3^- is the compensatory response to this transient hypercapnia, and thus reflects a post-hypercapnic status. Serum HCO_3^- concentrations would increase as a result of the rise, albeit transient, in P_{aCO_2}, and the impaired ability of the kidneys to increase renal excretion of HCO_3^-, shown in this study, would contribute to persistent elevation of serum HCO_3^-. However, while the present study did not investigate the potential role of compensatory mechanisms, the elevated urinary chloride concentration would suggest that post-hypercapnic metabolic alkalosis is not the main mechanism in play.

The lack of compelling data to suggest alternative mechanisms for the metabolic alkalosis and increased serum HCO_3^-, such as post-hypercapnic state or dehydration, together with the discrepancies in urinary secretion of chloride and HCO_3^-, point to a potential defect in renal handling of HCO_3^-, possibly secondary to CFTR dysfunction in the kidneys. In normal physiological conditions, the chloride/HCO_3^- exchanger pendrin is up- and downregulated on the basis of serum HCO_3^- concentrations, and plays a major role in controlling chloride absorption [9]. Wild-type CFTR is central to the regulation of pendrin expression, and its dysfunction might be contributing to the reduced excretion of HCO_3^- *via* the kidneys. This is supported by a recent CF mouse model, which identified a link between inactivation of pendrin and reduced urinary alkalinisation [10, 11]. In addition, it was recently shown that following an acute base load, a handful of individuals with CF was unable to acutely increase the excretion of HCO_3^-, in a process which was partially reversed by CFTR modulators [11], suggesting therefore that CFTR dysfunction in the kidneys and the interaction with pendrin are central in the regulation of HCO_3^- and acid-base status.

Metabolic alkalosis and increased serum HCO_3^- in CF have been considered potential risk factors for worsening underlying hypercapnic respiratory failure [7]. This does not appear to be the case in our cohort, as P_{aCO_2} distribution is within the normal range, albeit at the upper limit of normality in the CF cohort. While this could be a reflection of lower lung function and perhaps reduced ventilation, especially at night and during exertion [14], the impaired ability to increase urinary excretion of HCO_3^- might contribute to or cause the hypoventilation itself, as recently shown in the CFTR knockout mice [15].

In conclusion, in CF, the aetiology of metabolic alkalosis, isolated elevation of serum HCO_3^- and, more in general, of the acid-base disturbances is complex in nature and appears to be driven, in part, by renal tubular CFTR dysfunction and its role in chloride reabsorption and HCO_3^- excretion. However, a possible compensatory response to hypercapnia cannot be ruled out as the use of urinary chloride concentration in the differential of metabolic alkalosis might be over-simplistic in the context of a condition such as CF. Further larger studies are feasible and necessary to characterise the effects of treatment CFTR modulators on renal handling of HCO_3^- and electrolytes, and the potential role of transient hypercapnia in driving the increase in serum HCO_3^- during pulmonary exacerbations and clinical stability.

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References

1 Devlin J, Beckett NS, David TJ. Elevated sweat potassium, hyperaldosteronism and pseudo-Bartter's syndrome: a spectrum of disorders associated with cystic fibrosis. *J R Soc Med Suppl* 1989; 82: 38–43.
2 Fustik S, Pop-Jordanova N, Slaveska N, *et al.* Metabolic alkalosis with hypoelectrolytemia in infants with cystic fibrosis. *Pediatr Int* 2002; 44: 289–292.
3 Dahabreh M, Najada A. Pseudo-bartter syndrome, pattern and correlation with other cystic fibrosis features. *Saudi J Kidney Dis Transpl* 2013; 24: 292–296.
4 Pollard K, Daniels TE, Etherington C, *et al.* Capillary blood gas sampling at annual assessment – a service review. *J Cyst Fibros* 2010; 9: S85.
5 Baird JS, Walker P, Urban A, *et al.* Metabolic alkalosis and cystic fibrosis. *Chest* 2002; 122: 755–756.

6 Al-Ghimlas F, Faughnan ME, Tullis E. Metabolic alkalosis in adults with stable cystic fibrosis. *Open Respir Med J* 2012; 6: 59–62.
7 Holland AE, Wilson JW, Kotsimbos TC, *et al.* Metabolic alkalosis contributes to acute hypercapnic respiratory failure in adult cystic fibrosis. *Chest* 2003; 124: 490–493.
8 Kunzelmann K, Schreiber R, Hadorn HB. Bicarbonate in cystic fibrosis. *J Cyst Fibros* 2017; 16: 653–662.
9 Soleimani M. The multiple roles of pendrin in the kidney. *Nephrol Dial Transplant* 2015; 30: 1257–1266.
10 Berg P, Svendsen SL, Hoang TTL, *et al.* Impaired renal HCO_3^- secretion in CFTR deficient mice causes metabolic alkalosis during chronic base-loading. *Acta Physiol (Oxf)* 2020; 231: e13591.
11 Berg P, Svendsen S, Sorensen M, *et al.* Impaired renal HCO_3^- excretion in cystic fibrosis. *J Am Soc Nephrol* 2020; 31: 1711–1727.
12 Gamble JL. Carbonic acid and bicarbonate in urine. *J Biol Chem* 1922; 51: 295–310.
13 Gillion V, Jadoul M, Devuyst O, *et al.* The patient with metabolic alkalosis. *Acta Clin Belgica Int J Clin Lab Med* 2019; 74: 34–40.
14 Bradley S, Solin P, Wilson J, *et al.* Hypoxemia and hypercapnia during exercise and sleep in patients with cystic fibrosis. *Chest* 1999; 116: 647–654.
15 Berg P, Andersen JF, Sorensen MV, *et al.* Alkalosis-induced hypoventilation in cystic fibrosis: the importance of efficient renal adaptation. *Proc Nat Acad Sci U S A* 2022; 119: e2116838119.