Journal of Cystic Fibrosis 13 (2014) 528–533

www.elsevier.com/locate/jcf

Original Article

Sweat conductivity: An accurate diagnostic test for cystic fibrosis?☆

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Received 17 September 2013; received in revised form 23 December 2013; accepted 9 January 2014
Available online 31 January 2014

Abstract

Background: Sweat chloride test is the gold standard test for cystic fibrosis (CF) diagnosis. Sweat conductivity is widely used although still considered a screening test.

Methods: This was a prospective, cross-sectional, diagnostic research conducted at the laboratory of the Instituto da Criança of the Hospital das Clínicas, São Paulo, Brazil. Sweat chloride (quantitative pilocarpine iontophoresis) and sweat conductivity tests were simultaneously performed in patients referred for a sweat test between March 2007 and October 2008. Conductivity and chloride cut-off values used to rule out or diagnose CF were <75 and ≥ 90 mmol/L and <60 and ≥ 60 mmol/L, respectively. The ROC curve method was used to calculate the sensitivity, specificity, positive (PPV) and negative predictive value (NPV), as well as the respective 95% confidence intervals and to calculate the area under the curve for both tests. The kappa coefficient was used to evaluate agreement between the tests.

Results: Both tests were performed in 738 children, and CF was ruled out in 714 subjects; the median sweat chloride and conductivity values were 11 and 25 mmol/L in these populations, respectively. Twenty-four patients who had received a diagnosis of CF presented median sweat chloride and conductivity values of 87 and 103 mmol/L, respectively. Conductivity values above 90 mmol/L had 83.3% sensitivity, 99.7% specificity, 90.9% PPV and 99.4% NPV to diagnose CF. The best conductivity cut-off value to exclude CF was <75 mmol/L. Good agreement was observed between the tests (kappa: 0.934).

Conclusions: The sweat conductivity test yielded a high degree of diagnostic accuracy and it showed good agreement with sweat chloride. We suggest that it should play a role as a diagnostic test for CF in the near future.

Keywords: Cystic fibrosis; Sweat test; Conductivity; Pilocarpine

1. Introduction

The sweat test remains the gold standard test for diagnosis of cystic fibrosis (CF) despite the identification of over 1900 mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene [1]. CF is confirmed when sweat chloride values are ≥ 60 mmol/L, when two CF-causing mutations are detected or when there is increased nasal potential difference associated with the clinical phenotypic features of the disease [2–5]. The diagnosis criteria for CF have been revised, and new reference values for sweat chloride have been established for infants younger than 6 months: normal values are lower than

☆ The preliminary results of this study were presented at the 8th International Congress on Pediatric Pulmonology, March 29–31, 2008, Nice, France, at the II Brazilian Congress of Cystic Fibrosis. May 7–10, 2008, in Salvador, Brazil and at the 22nd Annual North American Cystic Fibrosis Conference, October 23–25, 2008, Orlando, USA. The preliminary results of this study have previously been published in abstract form (Pediatric Pulmonology 2008;43, Suppl.31:p278).

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http://dx.doi.org/10.1016/j.jcf.2014.01.002

30 mmol/L and borderline values are between 30 and 59 mmol/L [5–7].

In 1959, Gibson and Cooke developed the measurement of sweat chloride concentration by the quantitative pilocarpine iontophoresis test (QPIT) method and tested 25 CF patients and 64 controls [8]. The CF patients' sweat chloride values were ≥ 80 mEq/L and none of the controls had sweat chloride values greater than 60 mEq/L. Since then, the measurement of sweat chloride by the QPIT has been considered the gold standard method to diagnose CF. However, this test is cumbersome to perform and requires the weighing of the sweat sample, elution of sweat from the filter paper or gauze used to collect it and chemical analysis of electrolytes after dilution of the sweat sample [9]. The procedure is vulnerable to errors if not performed by experienced professionals who are specifically trained in sweat collection and analysis. In the past years it has become common in many CF centers to use the macroduct® coils for sweat collection keeping the quantitative analysis of chloride, which makes QPIT easier [10].

The conductivity sweat test is a simpler sweat test method that eliminates the weighing and dilution steps and also reduces the risk of sample evaporation. Studies comparing the QPIT to the conductivity test have been conducted since late 1950 and have shown good correlation and agreement between chloride and conductivity values [11–21]. It should be emphasized that the reference values for sweat conductivity are different from those for sweat chloride because of the presence of unmeasured anions such as lactate and bicarbonate when sweat conductivity is analyzed, although the test does reflect the concentration of sodium chloride as the primary sweat component. As a result, sweat conductivity values are approximately 15 mmol/L higher than sweat chloride values. Values higher than 90 mmol/L support a CF diagnosis [20], although the manufacturer of sweat conductivity equipment recommends values higher than 80 mmol/L as diagnostic [22].

CF is frequently under-diagnosed and/or diagnosed late in Brazil, partly because of the complexity of the sweat test and the scarcity of professionals trained to properly conduct the QPIT.

The objective of the present study was to compare sweat chloride values obtained by the QPIT with sweat conductivity values collected using the macroduct® system in a sample of patients being investigated for CF and to assess the accuracy of the conductivity test as a diagnostic procedure.

2. Methods

This study was a prospective, cross-sectional, diagnostic research conducted at the laboratory of the Instituto da Criança of the Hospital das Clínicas, São Paulo, Brazil, from March 2007 to October 2008. This is a referral laboratory for the sweat test that follows the British guidelines [23]. All patients referred to the laboratory in the study period for a sweat test because of a suspicion of CF were invited to participate. An inclusion criterion was a sufficient sweat sample with both techniques. Exclusion criteria were patients doing a repeat sweat test to avoid bias in the sensitivity and specificity results and patients on oral steroid therapy. This study was approved by the Human Ethics Committee of the Hospital das Clínicas of the Medical School of the University of São Paulo (approval number 609/04). Written informed consent was obtained from all subjects or their parents.

Both types of sample were collected at the same time from each of the patients' forearms as described below:

3. Sweat collection

3.1. Classic sweat test: QPIT collected onto filter paper (Gibson & Cooke technique)

The skin of the forearm was cleaned by using distilled water and dried with gauze. Copper electrodes 2.5 × 2.5 cm were then placed on the skin using strapped-on gauze embedded in 0.5% pilocarpine nitrate solution (positive electrode) and sulfuric acid 0.004 N (negative electrode). A current of 2 to 5 mA was applied for 5 min. After iontophoresis was completed, the electrodes were removed and the skin was cleaned again with distilled water and dried with gauze. Then, a disk of filter paper of 4.2 cm (Whatman filter paper number 42) was removed from a previously weighed bottle, placed over the area that was iontophoresed and covered with a plastic square and adhesive tape. After 30 min, the moist filter paper was removed, returned to the bottle and reweighed by using an analytical scale to measure the mass of the sweat. The minimum accepted sample weight was 75 mg. The paper was then placed inside a glass container, which was sealed with plastic to be sent to the laboratory for chloride analysis (coulometric titration using a digital chloridometer – Labconco®). The sweat was eluted from the filter paper with 10 ml of distilled water.

3.2. Sweat conductivity test: macroduct® sweat collection system with analysis of electrolytes based on conductivity

The skin of the forearm was cleaned by using 70% alcohol followed by distilled water and wiped clean using gauze. This cleaning step was followed by sweat stimulation using electrodes with pilocarpine gel disks (Pilogel®) applied over the skin and the passage of an electric current of 1.5 mA for 5 min. After iontophoresis, the area was cleaned with distilled water and wiped, and the macroduct® collector was then tightened by using straps. Sweat collection lasted for 30 min and a minimum amount of 15 μl was required. After the collection process, the catheter was separated from the disk and a syringe was connected to one end of the catheter. The other end was connected to the Sweat-Chek® analyzer device, which measured the conductivity of the sample and converted the measured values into sodium chloride molarity unit equivalents. The value of conductivity was that when the reading was stabilized for approximately 10 s. The Sweat-Chek® analyzer measurements were regularly verified by using standard Wescor® NaCl standard sweat controls (with approximately 40, 70 and 130 mmol/L). When the reading given by the analyser did not agree with the specified molarity of the standard solution recalibration was performed with a calibrator solution (90 mmol/L) according to the manufacturer recommendations.

The conductivity cell was cleaned with distilled water, followed by bursts of air to purge any remaining droplets, between the tests. Conductivity was measured at 23 °C and the principal investigator performed all the tests. The technician who performed the chloride measurements was not aware of the conductivity test results.

A CF diagnosis was established when the chloride concentration was ≥60 mmol/L in two sweat samples associated with a clinical CF phenotype. A CF diagnosis was also established when borderline sweat chloride values were associated with a clinical CF phenotype or when borderline values were accompanied by two disease-causing CFTR gene mutations. CF was ruled out when the chloride concentration was less than 40 mmol/L (less than 30 mmol/L in infants up to 6 months old) and the child did not fulfill the clinical criteria for a CF diagnosis.

4. Statistical analysis

Conductivity cut-off values to rule out or diagnose CF were set at <75 and ≥90 mmol/L, respectively, and the chloride cut-off values were <60 and ≥60 mmol/L. These cut-off values of conductivity were selected based on the largest study by Lezana et al. comparing both sweat test techniques [20]. Borderline values for conductivity were defined as 75 to 89 mmol/L and those for sweat chloride were defined as 40 to 59 mmol/L.

Receiver operator characteristic (ROC) curves were constructed (MedCalc® program version 11.2.0.0) to calculate the sensitivity, specificity, positive (PPV) and negative predictive values (NPV) and respective 95% confidence intervals (95CI%) of the conductivity test and also to calculate the area under the curve for the two tests in order to assess their accuracy. Kappa coefficient was calculated to evaluate the agreement between the two tests.

This was a diagnostic research questioning if the test in study would distinguish patients with and without CF among patients in whom it was clinically reasonable to suspect of CF [24]. As we hypothesized that we would have only around 10 diagnosis of CF in the study period, we planned to perform around 700 tests in order to achieve good sensitivity, specificity, PPV and NPV for the conductivity test and not to have an unstable confidence interval.

5. Results

Both types of sweat test were simultaneously performed on the forearms of 738 patients. CF was ruled out in 714 (96.7%) patients, whereas CF was diagnosed in 24 patients (3.3%). The clinical characteristics of the 714 patients without CF are described in Table 1.

Median sweat chloride and conductivity values of 11 and 25 mmol/L, respectively, were observed in these 714 patients without CF (Table 2). Sweat conductivity values were equal to or greater than 90 mmol/L in three patients without a clinical CF phenotype and they represent the false-positive tests (Table 3).

Of the 714 patients without CF, excluding the three false-positive results mentioned above, conductivity values were equal to or higher than 50 mmol/L in only 37 patients (5.2%), and only three had values between 75 and 89. Only 43 infants without CF were less than 6 months old (excluding the patient with pseudohypoaldosteronism), and a sweat conductivity higher than 50 mmol/L (54 mmol/L) was observed in only one case with a normal concomitant sweat chloride value.

Table 1
Characteristics of the patients.

	Non-CF patients (n = 714)	CF patients (n = 24)
Age (years), mean ± SD	4.2 ± 4.2	3.6 ± 4.1
Median (range)	2.5 (0.1 a 19.2)	2.4 (0.1 to 13)
Male sex, n (%)	399 (56%)	15 (62.5%)
Ethnicity, n (%)		
Caucasians	569 (79.7%)	21 (87.5%)
African descent	136 (19%)	3 (12.5%)
Asian descent	9 (1.3%)	–
Referral diagnosis, n (%)		
Wheezing baby	200 (28.1%)	1 (4%)
Asthma	170 (24%)	2 (8.5%)
Upper and/or lower respiratory symptoms and/or digestive symptoms	122 (17%)	–
Recurrent pneumonia	116 (16.2%)	–
Failure to thrive	47 (6.5%)	–
Family history of CF	20 (2.8%)	3 (12.5%)
Chronic diarrhea	16 (2.2%)	–
Bronchiectasis	12 (1.7%)	–
Chronic cough	11 (1.5%)	2 (8.5%)
Positive newborn screening	–	6 (25%)
Rectal prolapse	–	1 (4%)
Not available	–	9 (37.5%)

The clinical characteristics of the 24 patients with CF are shown in Table 1. Median sweat chloride and conductivity values of 87 and 103 mmol/L, respectively, were observed in these patients, of whom 11 were less than 6 months of age (Table 2). Three patients had sweat conductivity values less than 90 mmol/L and they represent the false-negative tests (Table 3).

A comparison was made between males and females (CF and non-CF) in both sweat conductivity and chloride and no differences were found (Table 4).

The sensitivity, specificity, PPV and NPV for a CF diagnosis when sweat conductivity values were ≥90 mmol/L are shown in Table 5. With sweat conductivity values less than 75 mmol/L, a CF diagnosis could very likely be ruled out (99.7% NPV; 95%CI: 99.0–100%). A very large area under the curve was found in the ROC curve analysis, which demonstrates that the values determined by using the conductivity method closely matched the chloride test values (Fig. 1). Excellent agreement was found

Table 2
Sweat chloride and sweat conductivity in non-CF and CF patients.

	Non-CF patients (n = 714)		CF patients (n = 24)	
Sweat tests (mmol/L)	Chloride	Conductivity	Chloride	Conductivity
Median	11	25	87	103
Mean ± SD	13.4 ± 8.7	28.3 ± 12	90.3 ± 20	99.7 ± 18
Range	3–137	14–138	54–132	50–126

Table 3
False positive and false negative sweat conductivity test.

Sweat tests (mmol/L)	Chloride	Conductivity
Dyshidrosis	55	98
Pseudohypoaldosteronism	137	138
Chronic sinusitis	47	90
Atypical CF — case #1	54	57
Atypical CF — case #2	56	50
CF	83	85

between the sweat chloride and conductivity methods, with a kappa value of 0.934 (95% CI: 0.86–1.009).

6. Discussion

The main result of our study was to show that the conductivity sweat test is an accurate, highly sensitive and specific method with a high capacity to discriminate between CF and non-CF subjects. Good agreement was observed between the sweat chloride and conductivity methods.

The conductivity method was applied in 738 subjects with clinically suspected CF: CF was ruled out in 714 patients and diagnosed in 24. In the 714 non-CF patients, only three tests had false-positive results: conductivity values of 138, 98 and 90 mmol/L and chloride values of 137, 55 and 47 mmol/L, respectively. In these cases, the diagnoses were pseudohypoaldosteronism, which is a condition associated with false-positive sweat chloride results, dyshidrosis and chronic sinusitis. The patient with chronic sinusitis might represent a mild CF spectrum disease. As two additional sweat chloride tests for this patient were in the normal range, chest computed tomography (CT) and spirometry were normal, as well as the nutritional status, CF was ruled out.

Three conductivity tests were false-negative: two patients had a diagnosis of atypical CF based on borderline sweat chloride values and clinical features of CF. One was a patient with pancreatic insufficiency, bronchiectasis, *Pseudomonas aeruginosa* in the sputum and severe airway obstruction on spirometry. His sweat chloride was 56 and conductivity of 50 mmol/L. Two other sweat chloride tests had values of 41 and 28 mmol/L. Only the p.F508del and the p.G542X mutations were analyzed and were not found. He is in regular follow up at this CF clinic and is receiving specific treatment for CF. The other patient had an initial diagnosis of wheezing baby, had no pancreatic insufficiency or specific lung pathogens and one p.G542X mutation was found. Her sweat chloride was 54 and conductivity of 57 mmol/L. A second measured sweat chloride value was 53 mmol/L. She is being treated with inhaled steroids for asthma, but CF was not ruled out. The third case (sweat chloride of 83 and conductivity of 85 mmol/L) was a CF patient with no respiratory symptoms thus far, with pancreatic sufficiency and with one p.F508del mutation. An extended CFTR mutation analysis has not yet been performed in these three patients. These three cases reinforce the notion that the diagnosis of CF in any patient will require clinical evaluation, a sweat test and genetic testing and that patients with borderline sweat tests (either chloride or conductivity) always pose a diagnostic challenge, besides raising the issue of the appropriate cut-off values for diagnostic categories for both techniques.

Table 5
Sensitivity and specificity of the sweat conductivity and sweat chloride tests.

	CF patients		Non-CF patients	
	Conductivity	Chloride	Conductivity	Chloride
Positive test	21	22	3	1
Negative test	3	2	711	713
Total	24	24	714	714

95%CI = 95% confidence interval; PPV = positive predictive value; NPV = negative predictive value. ROC curve for conductivity: sensitivity = 83.3% (95%CI: 62.6–95.2); specificity = 99.7% (95%CI: 99.0–100); PPV = 90.9% (95%CI: 70.8–98.6); NPV = 99.4% (95%CI: 98.6–99.8). Borderline values for both conductivity and chloride were taken as negative.

Several studies have already demonstrated an excellent agreement between sweat chloride and conductivity, and their results are summarized in Table 6. All of these studies have concluded that the sweat conductivity method is as effective as the chloride test in the laboratory diagnosis of CF with a similar ability to distinguish patients with or without CF. The main criticism of conductivity is that it does not measure chloride ions alone but sodium chloride, besides lactate and bicarbonate and this might impair a CF diagnosis. Physicians should pay attention on the reference values for sweat conductivity, that are different from sweat chloride, when analyzing a sweat test result.

Nanoduct® is a new diagnostic system that induces, collects and analyzes sweat conductivity in one step. Two studies in large populations, including infants with positive newborn screening for CF, also demonstrated this method to be a good diagnostic test compared to sweat chloride to diagnose or rule out CF [25,26].

A cut-off point of 90 mmol/L for a CF diagnosis was chosen based on the largest study comparing both sweat test techniques. Lezana et al. [20] studied 3834 patients and found a high correlation between the methods with regard to their ability to confirm and to rule out CF. In 3540 patients without CF, the authors found a median conductivity of 36 mmol/L, and in 294

Table 4
Sweat chloride and sweat conductivity among CF and non-CF female and male subjects.

	Non-CF patients				CF patients			
Sweat tests (mmol/L)	Chloride		Conductivity		Chloride		Conductivity	
Gender	Female	Male	Female	Male	Female	Male	Female	Male
Median	10	12	26	25	87	87	96	104
Mean ± SD	13.4 ± 10	13.3 ± 7	29.5 ± 14	27.3 ± 9	89.5 ± 22	90.8 ± 20	97.1 ± 18	101.2 ± 18
Range	3–137	3–51	14–138	15–75	54–132	56–129	57–117	50–126

Number of subjects: non-CF female = 315; CF female = 9; non-CF male = 399; CF male = 15

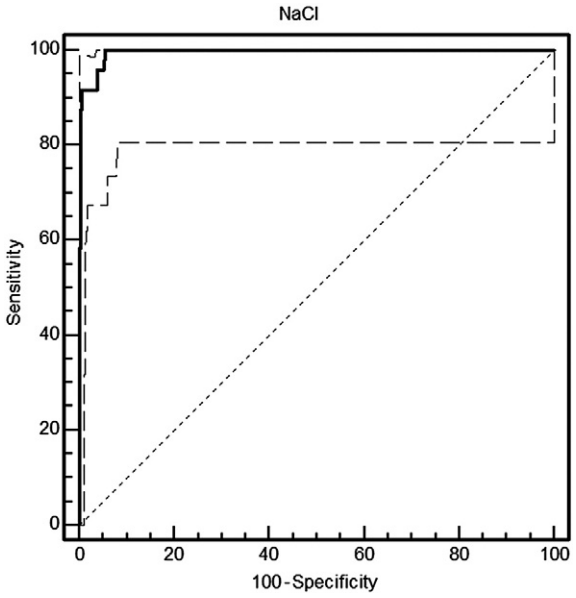

Fig. 1. The ROC (receiver operating characteristics) curve obtained for 738 subjects to assess the capacity of conductivity (NaCl = sodium chloride) to predict a cystic fibrosis diagnosis. Solid line: area under the curve for conductivity (99.4%). Dashed line: 95% confidence interval (98.6–99.8%).

patients with CF the median conductivity was 111 mmol/L. These authors found that the conductivity cut-off value for optimal prediction of a positive CF diagnosis was ≥90 mmol/L, which was associated with a greater than 99% sensitivity, specificity, PPV and NPV. Similarly, the conductivity cut-off value for optimal prediction of a negative CF diagnosis was <75 mmol/L, with 93% NPV. When we used the same cut-off values as Lezana et al., we observed that with a conductivity value higher than 90 mmol/L, we had greater than 80% sensitivity, specificity, PPV and NPV for a CF diagnosis. Most importantly, with a sweat conductivity value lower than 75 mmol/L, CF could very likely be ruled out (NPV 99.7%). A very large area under the curve in the ROC analysis was found, which demonstrates that the conductivity method closely matched the sweat chloride method. When we set the cut-off point for conductivity at 80 mmol/L for a CF diagnosis, an increase in sensitivity (92%) occurred concomitantly with a decrease in the PPV (85%), whereas the test retained good specificity and NPV (above 99%).

If we followed the CF Foundation recommendation, that is, to perform a QPIT in all patients that present with a sweat conductivity value ≥50 mmol/L, a QPIT should have been performed in only 37 non-CF patients based on conductivity values between 50 and 89 mmol/L. This strategy would save our sweat test laboratory from performing 674 QPITs.

Although there is a lower incidence of CF in Brazil (estimates of 1 in 7576 live births) compared to European and North American countries [27] CF newborn screening is increasingly being implemented in our country using the IRT/IRT (immunoreactive trypsinogen) algorithm, and so the demand for sweat testing has tremendously increased because of numerous false-positive results generated by this algorithm. In Brazil, the QPIT is mainly performed in laboratories of university hospitals linked to a CF center, such as ours. With this increased demand for sweat testing, conductivity could be evaluated as the first sweat test in these infants and also in other patients referred for a sweat test because of a clinical suspicion of CF. When values are between 50 and 79 mmol/L, QPIT and chloride analysis should be performed in an accredited CF center. When two sweat conductivity tests return values higher than 80 mmol/L and there are clinical features of the disease, a CF diagnosis can be established. This strategy would prevent under-diagnosis and also prevent delayed CF diagnoses.

Although the QPIT is still traditionally used to confirm a diagnosis of CF, sweat conductivity should be considered an alternative test for a CF diagnosis [28,29], as it has already been compared to sweat chloride in over 6000 patients and has demonstrated good agreement with sweat chloride testing. Staff responsible for sweat conductivity evaluation should gain sufficient experience and familiarity with the test and maintain their expertise by performing this technique regularly. Accuracy in sweat collection with quantity verification, instrument calibration, cell cleaning and drying, avoiding cell infiltration by air bubbles and other delicate steps requires experienced and responsible staff to ensure the accuracy of the conductivity result [30]. Setting the positive cut-off value at 80 mmol/L, as recommended by the

Table 6
Studies comparing sweat conductivity with sweat chloride in CF and non-CF patients.

Study	Number of CF patients	CF patients		Number of non-CF patients	Non-CF patients		Statistics
		Mean conductivity (mmol/L)	Mean chloride (mmol/L)		Mean conductivity (mmol/L)	Mean chloride (mmol/L)	
Hammond et al. [16].	43	113.1	98.8	471	33.4	16.4	r = 0.974
Mastella et al. [17].	103	112	95.7	184	39.8	16.3	r = 0.988
Heeley et al. [18].	57	110	99	154	37	14	Not mentioned *
Riedi et al. [19].	31	118.5	113.2 (sodium)	175	40.9	36.3 (sodium)	r = 0.99
Lezana et al. [20].	294	111 (median)	Not mentioned	3540	36 (median)	Not mentioned	Kappa coefficient = 0.998
Mattar et al. [21].	52	119.7	110.5	50	34.4	17.4	Area under the ROC curve: 100% (95CI%: 96.4–100%)

R = correlation coefficient; ROC = receiver operator characteristic; CI = confidence interval;
* Equivocal results: conductivity — 1:57 CF, 2:154 non-CF; chloride — 1:57 CF, 1:154 non-CF.

manufacturer, may be safer than setting the cut-off at 90 mmol/L to not miss a CF diagnosis, and we suggest that values between 50 and 79 mmol/L should be considered borderline and that these patients should undergo a QPIT for a chloride analysis.

In conclusion, sweat conductivity showed an excellent capacity to discriminate between CF and non-CF subjects with a high degree of diagnostic accuracy, and it showed good agreement with sweat chloride. It is our view that sweat conductivity should play a role as a diagnostic test for CF in the near future.

Acknowledgments

We thank Wescor® Inc. Biomedical, Utah, USA who donated the Macroduct® (sweat collection system) and Sweat Chek® (sweat conductivity analyzer) to Instituto da Criança, Hospital das Clínicas, United Medical Ltda. and Laboratório Roche, who donated the kits for the sweat conductivity test. These companies did not participate in the design of the study or in the analyses of the results. We thank Cresio R. Pereira, MD, PhD, who helped to delineate the study and also for epidemiological assistance. We also thank Karina H. Kawasato, Biomedical, MSc, who performed all chloride analysis.

Editorial Assistance

This manuscript was edited for proper English language, grammar, punctuation, spelling, and overall style by editors at the American Journal Experts (Certificate Verification Key: D4E7-EE4B-25EA-558B-74D6), which were payed by the University of São Paulo – School of Medicine (PROAP fund – CAPES).

Conflict of interest statement

The authors have no conflicts of interest to disclose.

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