

# Comparison between classic Gibson and Cooke technique and sweat conductivity test in patients with and without cystic fibrosis

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## Abstract

**Objective:** To compare sweat chloride values obtained by quantitative pilocarpine iontophoresis (classic test) with the sweat conductivity values obtained using Macroduct® collection system in patients with and without cystic fibrosis (CF). The cost and time spent to carry out each test were also analyzed.

**Methods:** The sweat test using both techniques was performed at the same time in patients with and without CF. Conductivity cutoff values to rule out or diagnose CF were < 75 and ≥ 90 mmol/L, respectively, and for the classic test the chloride values were < 60 and ≥ 60 mmol/L.

**Results:** Fifty-two patients with CF (29 males and 23 females; aged from 1.5 to 18.2 years) underwent the sweat test using both techniques, showing median sweat chloride and conductivity values of 114 and 122 mmol/L, respectively. In all of them, conductivity was ≥ 95 mmol/L, which provided the test with 100% sensitivity (95%CI 93.1-100). Fifty patients without CF (24 males and 26 females; aged from 0.5 to 12.5 years) had median sweat chloride and conductivity values of 15.5 and 30 mmol/L, respectively. In all cases, conductivity was < 70 mmol/L, which provided the test with 100% specificity (95%CI 92.9-100). Time spent to perform the tests was significantly shorter for the conductivity test, and its cost was also lower.

**Conclusions:** The conductivity test showed high sensitivity and specificity, and there was good correspondence between the tests. The time spent to carry out the conductivity test was shorter and the cost was lower in comparison with the classic test.

*J Pediatr (Rio J). 2010;86(2):109-114: Cystic fibrosis, sweat test, conductivity, pilocarpine.*

## Introduction

Cystic fibrosis (CF) is an autosomal recessive genetic disease caused by mutations in one single gene located in the long arm of chromosome 7, affecting the epithelial cells of several organs, including the respiratory tract, exocrine pancreas, bowels, deferent channels, hepatobiliary system, and sudoriparous gland, resulting in alterations in several organs. CF is characterized by chronic suppurative lung disease, pancreatic failure, multifocal biliary cirrhosis, male infertility, and large sweat electrolytic loss.<sup>1-3</sup>

CF diagnosis is confirmed when sweat chloride values of two independent measurements are higher than 60 mmol/L, or when two mutations for CF are detected by means of genetic study, or even when there is alteration in the nasal potential difference measurement (a test that is performed at very few health care facilities) associated with a clinical picture compatible with the disease.<sup>4,5</sup> The diagnosis criteria for CF have been recently revised; therefore, for infants younger than 6 months, the normal values of sweat chloride

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This study was conducted at the Pulmonology Department, Instituto da Criança, Hospital das Clínicas, School of Medicine, USP, São Paulo, SP, Brazil.

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Conflict of interest: The material used in this study was donated by the companies Wescor® (Inc. Biomedical Utah, USA) (Macroduct® – sweat collection system – and Sweat Chek® – sweat conductivity analyzer), United Medical and Laboratório Roche (kits for the sweat conductivity test). These companies did not participate in the design of the project, in the development of the study, and in the analyses of the results.

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are lower than 30 mmol/L and the borderline values are between 30 and 59 mmol/L, since it has been found that in normal young infants sweat chloride values are around 10 mmol/L.<sup>6-8</sup> Sweat test is positive in 98 to 99% of the patients with CF, and it is used as the routine test for the diagnosis of this disease. The genetic study of mutations is a more expensive method and, even when it shows a normal result, it does not rule out CF diagnosis because it is possible to find more rare mutations that are not usually analyzed by the marketed kits that study the mutations for CF.

Although several techniques have been created for the collection and measurement of sweat electrolytes, the most reliable test is based on the pilocarpine iontophoresis technique described by Gibson & Cooke<sup>9</sup> in 1959, which is still considered to be the gold standard for CF diagnosis. However, this is a complex technique that requires the definition of the exact sweat weight using an analytical scale, and sweat evaporation must be avoided during sweat collection; in addition, the sweat sample needs to undergo biochemical analysis of electrolytes, a technique that is also quite complex. According to this method, it is necessary to collect at least 50 mg of sweat<sup>10,11</sup> (the ideal amount is  $\geq 75$  mg) so that an accurate result can be reached, which may be difficult in infants younger than 1 to 2 months. The procedure is vulnerable to errors, which may lead to false-positive and false-negative results if the test is not performed by experienced professionals specifically trained in sweat collection and analysis. The minimum number of tests that a laboratory must carry out to be qualified as a proficient lab in the sweat test performance has not been defined.<sup>11</sup> Some international guidelines recommend that labs perform at least between 50 and 100 tests per year, and each technician must carry out at least 10 tests per year.<sup>12,13</sup> In addition, inadequate sweat samples should not account for more than 5% of the total number of samples collected.<sup>12,13</sup> CF underdiagnosis rate is estimated to be high in Brazil, and this is partially due to the complexity of the sweat test, the small number of professional trained to carry out the test in Brazil, as well as the shortage of equipment for the adequate performance of the test.

In order to make the test simpler, many labs have been using alternative methods.<sup>14-21</sup> One of these methods includes the use of the device Macroduct<sup>®</sup> – a sweat collection system,<sup>22</sup> through which sweat is collected into a plastic coil after stimulation by pilocarpine iontophoresis. Weighting and risk of evaporation are thus eliminated. The sweat can be taken from the coil and its ionic composition can be later analyzed using the usual biochemical techniques, or it may be immediately placed in the conductivity analyzer – Sweat-Chek – Wescor<sup>®</sup>,<sup>22</sup> which will quickly provide the equivalent values of sweat sodium chloride (NaCl) in mmol/L.

The objective of the present study was to compare sweat chloride values obtained by the quantitative pilocarpine iontophoresis test (classic test) with sweat conductivity

values collected using the Macroduct<sup>®</sup> system in patients diagnosed with CF and in patients whose CF diagnosis had been ruled out, thus assessing the diagnostic properties of the test. Cost and time spent to perform the collection of the sweat sample and the measurements of electrolytes for each test were also assessed.

## Methods

During the first phase of the study, we invited patients with a CF diagnosis who were registered and followed at the pulmonology outpatient clinic of Instituto da Criança, Hospital das Clínicas, Universidade de São Paulo (USP), São Paulo, state of São Paulo, Brazil, to participate in the present study. After this initial phase, we invited other patients to take the test. These patients were also followed at the same outpatient clinic but had received other diagnosis (asthma, wheezing infant, etc) and whose CF diagnosis had been ruled out based on two normal sweat tests performed using the classic technique at the lab of Instituto da Criança and recorded on the patients' medical records.

The tests were carried out after the patients or their guardians received information about the study, read and signed the consent form. This research project was approved by the Research Ethics Committee of Hospital das Clínicas, School of Medicine, USP.

Both collections were conducted at the same time in each one of the patients' arms as described below:

### **a) Classic test: quantitative pilocarpine iontophoresis technique<sup>9</sup>**

First, the skin of the arm is cleaned using distilled water and wiped up using gauze. Next, 2.5 x 2.5 cm copper electrodes are placed on the skin using straps on gauze embedded in pilocarpine nitrate solution (positive electrode) and sulphur acid 0.004N (negative electrode). A current of 2 to 5 mA is applied during 5 minutes. Next, the skin is cleaned again using distilled water and wiped up using gauze for the placement of a filter paper of around 4 cm of diameter covered with plastic and masking tape. After 30 to 60 minutes, the paper is removed using tweezers and weighted using an analytical scale in order to check the sweat mass. Next, the paper is placed inside a glass container, which is sealed with plastic so that it can be sent for sodium and chloride laboratory analysis. Chloride concentration is measured using a digital chloridometer, and the sodium concentration is defined using a flame photometer (results in mmol/L). Sweat sodium is mainly useful as quality control, since discordant values between both ions suggest that there are problems related to the collection or analysis; therefore, they should not be interpreted alone.<sup>23,24</sup> The technician who performed the measurement of sodium and chloride was not aware of the result of the conductivity test.

**b) Sweat conductivity test: Macroduct® – sweat collection system – with analysis of electrolytes by means of conductivity<sup>22</sup>**

First, the skin of the arm is cleaned using distilled water and wiped up using gauze. Next, there is sweat stimulation using electrodes with pilocarpine gel discs (Pilogel®) over the skin and passage of an electric current during a period of 5 minutes at 1.5 mA. After iontophoresis, the area is cleaned and wiped up, and Macroduct® is tightened up using straps. The collector consists of a concave plastic disc with a central tiny orifice. This orifice is connected to a plastic catheter that is placed inside the disc in concentric circles. The sweat produced will be collected into this orifice and will be stored inside the catheter. A small amount of dye present in the collecting surface allows the stored sweat to be easily viewed, which makes it possible to quantify it in microliter. The sweat collection lasts for 30 minutes and, after the collection process, the catheter is separated from the disc and a syringe is connected to one end of the catheter. The other end is connected to the analyzer device Sweat-Chek®, which will measure the conductivity<sup>25</sup> of the sample collected and convert it into the equivalent of NaCl molarity.

**Statistical analysis**

This is a cross-sectional diagnostic test study called Phase II Questions,<sup>26,27</sup> that is, the test is performed in a population whose diagnosis is previously known: in patients with and without CF. It was possible then analyzed if the results obtained with the diagnostic test would be able to differentiate patients with the disease from normal patients and if the test would have a diagnostic potential (high sensitivity and specificity) under ideal conditions, that is, when it is previously known who has CF and who does not.

In order to check the sensitivity<sup>28</sup> of the conductivity test, the gold standard was the previously established CF diagnosis recorded on the patient's medical record, as well as the classic sweat tests showing altered results when the diagnosis was established. In order to check the specificity<sup>28</sup> of the conductivity test, the gold standard was the exclusion of the CF diagnosis based on two classic sweat tests previously performed showing normal results and presence of another diagnosis recorded on the medical record. A convenience sample of around 50 patients for each group was defined.

For sensitivity and specificity calculations, the cutoff points were: chloride normal value was < 60 mmol/L and CF diagnosis value was ≥ 60 mmol/L for the classic test, and conductivity normal value was < 90 mmol/L and CF diagnosis value was ≥ 90 mmol/L.

The following diagnostic properties were calculated using contingency tables: sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV),

and the respective 95% confidence intervals (95%CI) both for the conductivity and classic tests. Fisher's exact test was used to assess the association between the tests and the presence or absence of CF.

We used the receiver operator characteristic (ROC) curve<sup>28</sup> to calculate the area under the curve between both tests to assess their accuracy.

Wilcoxon test was used to compare the time spent to perform each test, with the significant difference set at  $p < 0.05$ .

**Results**

Both sweat collection techniques were conducted in 141 patients selected at the pulmonology outpatient clinic of Instituto da Criança between February 2006 and February 2007; 75 of these patients had CF and 66 did not have the disease.

Of the 75 patients with CF, 23 (31%) were not able to collect enough sweat by means of the classic test, while only four (5%) of them could not collect enough sweat using the conductivity test. Of the 66 patients without CF, 16 (24%) were not able to collect enough sweat by means of the classic test, while only two (3%) of them could not collect enough sweat using conductivity. These cases were excluded from the comparative analysis.

In 52 patients with CF, aged between 1.5 and 18.2 years, 29 males and 23 females, it was possible to perform both sweat test techniques, with median sweat chloride value and sweat conductivity value of 114 and 122 mmol/L, respectively, which evidenced an excellent correspondence between the tests (Table 1). All patients with CF had sweat conductivity values higher than 90 mmol/L, providing the test with 100% sensitivity. Three patients with a previous CF diagnosis had the result for the classic test lower than 60 mmol/L (normal in two of them and borderline in one case).

We could carry out both sweat test techniques in 50 patients without CF, aged between 6 months and 12.5 years, 24 males and 26 females, and we found median sweat chloride value and sweat conductivity of 15.5 and 30 mmol/L, respectively (Table 1). All patients without CF had sweat conductivity values lower than 75 mmol/L, providing the test with 100% specificity. One patient had a chloride value above 60 mmol/L according to the classic test, but when the test was performed again, the result was normal, and the conductivity for this case was lower than 75 mmol/L.

We found a strong association between CF and positivity in the sweat conductivity test and between absence of CF and negativity in the conductivity test ( $p < 0.0001$ ).

Diagnostic properties of both tests are described in Tables 2 and 3.

Comparing both tests using the ROC curve, the conductivity test included 100% of the area under the curve (95%CI 96.4-100), whereas the classic test included 99.9% of the area under the curve (95%CI 96.1-100), and the curves were overlapping (Figure 1).

The estimated cost of the classic test, calculated by the management of the Clinical Analyses Lab of Instituto da Criança was approximately R\$ 39.00 (US\$ 22.00). This calculation included the material used – solutions, gauzes, filter paper, gloves, etc. –, as well as the manpower used to collect the sweat. The sweat conductivity test, including the collection and analysis of conductivity, had a cost of approximately R\$ 36.00 (US\$ 20.00), considering the kits used to perform the test, calibrating solutions, gauzes, and gloves, and the same manpower included in the collection of the classic test.

The total time spent to perform the conductivity test (collection and analysis) ranged from 38 to 71 minutes, with a median of 45 minutes. On the other hand, for the classic test, the sweat collection alone took from 38 to 95 minutes, with a median of 50 minutes. Using the Wilcoxon test, the difference of time spent for both tests, considering only the collection time, was significant ( $p < 0.0001$ ). Considering also that the measurement of electrolytes conducted using the classic method at the lab of Instituto da Criança takes around 180 minutes, the difference of time for total performance of this test is even much higher.

## Discussion

In the present study, the sweat conductivity test showed to be highly sensitive and specific for CF diagnosis. Based

**Table 1 -** Sweat chloride and sodium values and conductivity in patients with and without cystic fibrosis

	Classic test (mmol/L)		Conductivity test (mmol/L)
	Chloride	Sodium	
Patients with CF (n = 52)			
Median	114	107	122
Mean ± SD	110.5±25.5	104.3±24.4	119.7±11.6
Minimum-maximum	37-165	36-158	95-138
Patients without CF (n = 50)			
Median	15.5	17	30
Mean ± SD	17.4±10	19.9±12.1	34.4±13.5
Minimum-maximum	6-61	3-67	14-69

CF = cystic fibrosis; SD = standard deviation.

**Table 2 -** Sensitivity and specificity of the conductivity test

	With CF	Without CF	Total
Positive test	52	0	52
Negative test	0	50	50
Total	52	50	102

95%CI = 95% confidence interval; CF = cystic fibrosis; NPV = negative predictive value; PPV = positive predictive value.

Sensitivity = 100% (95%CI 93.1-100); specificity = 100% (95%CI 92.9-100); PPV = 100% (95%CI 93.1-100);

NPV = 100% (95%CI 92.9-100).

$p < 0.0001$  (Fisher's exact test).

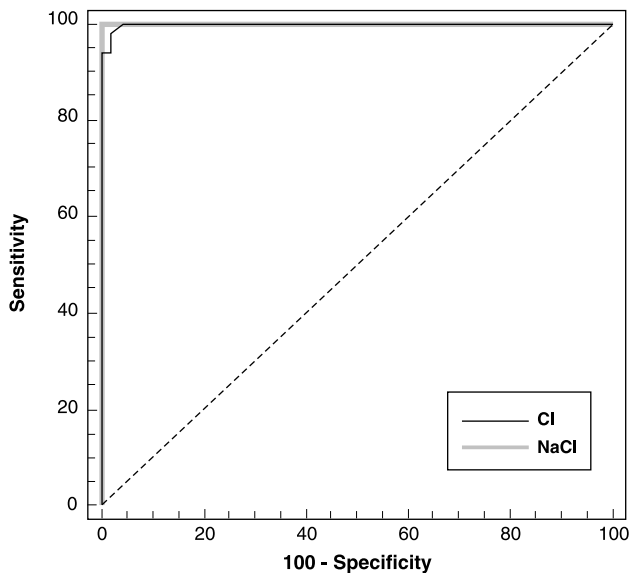
**Table 3 -** Sensitivity and specificity of the classic test

	With CF	Without CF	Total
Positive test	49	1	50
Negative test	3	49	52
Total	52	50	102

95%CI = 95% confidence interval; CF = cystic fibrosis; NPV = negative predictive value; PPV = positive predictive value.

Sensitivity = 94.2% (95%CI 84-98.8); specificity = 98% (95%CI 89.3-99.9); PPV = 98% (95%CI 89.4-99.9); NPV = 94.2% (95%CI 84-98.8).

$p < 0.0001$  (Fisher's exact test).



ROC = receiver operator characteristic.

**Figure 1** - Comparison of ROC curves: conductivity (NaCl) vs. chloride (Cl)

on the comparison of both tests using the ROC curve, we found that the conductivity test applied to our population was equivalent to the classic test, evidencing high accuracy.

We found an excellent correspondence between the classic and the conductivity tests in the patients with CF, with median sweat chloride and conductivity values of 114 and 122 mmol/L, respectively. In three patients with previous CF diagnosis, the result of the classic test was lower than 60 mmol/L, probably due to laboratory error, with sweat conductivity values higher than 90 mmol/L in all of them, showing that there were not false-negative results when we used the conductivity technique.

We also found an excellent correspondence between the classic and the conductivity tests in the patients without CF, with median sweat chloride and conductivity values of 15.5 and 30 mmol/L, respectively. In one patient, the chloride value obtained by the classic test was higher than 60 mmol/L. In this case, the sweat conductivity value was lower than 75 mmol/L, showing that there were not false-positive results when we used the conductivity technique.

Considering the diagnostic properties of both tests, we found that the 95%CI was narrower for the conductivity test when compared with the classic test, showing higher accuracy of the conductivity determination in our sample.

We decided to use a value of 90 mmol/L or higher as the cutoff point for the CF diagnosis based on the study by Lezana et al.<sup>20</sup> These authors compared both sweat test techniques (classic and conductivity) in 3,834 patients and found high correlation between the methods to confirm and to rule out the CF diagnosis ( $r = 0.6$ ;  $p < 10^{-6}$ ). In 3,540 patients without CF, the authors found a median conductivity of 36 mmol/L (ranging from 12 to 89 mmol/L), and in 294

patients with CF the median was 111 mmol/L (ranging from 82 to 148 mmol/L). These authors found that using the conductivity method the best cutoff point of sweat conductivity for CF diagnosis was 90 mmol/L or higher, with 99.66% of sensitivity, 100% of specificity, 100% of PPV, 99.97% of NPV, and a kappa value of 0.998.

Several studies have demonstrated an excellent correspondence between both methods. Hammond et al.<sup>17</sup> compared both techniques in patients without and with CF and found mean conductivity values of 33.4 mmol/L (ranging from 13 to 87 mmol/L) and mean sweat chloride values of 16.4 mmol/L (ranging from 5 to 60 mmol/L) in 471 patients without CF, and in 43 patients with CF the mean conductivity was 113.1 mmol/L (ranging from 90 to 136 mmol/L) and the mean chloride was 98.8 mmol/L (ranging from 77 to 117 mmol/L).

Mastella et al.<sup>18</sup> also found high correlation between both techniques by applying the tests to 287 individuals: 184 patients without CF had a mean chloride value of 16.3 mmol/L (ranging from 4 to 60 mmol/L) and a mean conductivity value of 39.8 mmol/L (ranging from 19 to 87 mmol/L), while 103 patients with CF had a mean chloride value of 95.7 mmol/L (ranging from 32 to 121 mmol/L) and a mean conductivity value of 112 mmol/L (ranging from 45 to 173 mmol/L). The conductivity test showed a similar ability to distinguish normal patients from patients with CF.

In Brazil, Riedi et al.<sup>21</sup> conducted sweat collections using Macroduct<sup>®</sup>, analyzing the same sample regarding conductivity and sodium levels, and found high correlation between the methods. They found mean sodium and conductivity values of 36.3 mmol/L (ranging from 12 to 75 mmol/L) and 40.9 mmol/L (ranging from 16 to 75 mmol/L), respectively, in 175 patients without CF, and 113.2 mmol/L (ranging from 80 to 146 mmol/L) and 118.5 mmol/L (ranging from 84 to 155 mmol/L) in 31 patients with CF. However, the literature recommends the measurement of the chloride levels for establishing the CF diagnosis instead of the measurement of the sodium levels alone.

The mean difference between the conductivity values compared with the chloride values, which is approximately 15 mmol/L higher for conductivity, occurs due to the presence of lactate, bicarbonate, and other unmeasured anions that are measured when the conductivity technique is used. Therefore, the cutoff value of sweat conductivity for CF diagnosis is higher when compared with the chloride cutoff value.

In the present study, using the conductivity technique, we could analyze the electrolytes in the sweat even when there were small amounts of sweat, which was not true for the classic method. Of the 141 tests performed, only six had an inadequate volume for the analysis of conductivity, while 39 tests were inadequate in terms of sweat mass for the analysis of chloride. The cause of the high rate of

inadequate sweat amount obtained by means of the classic test in our health care facility, which is a center of excellence for the sweat test and carries out an average of 75 tests a month, still needs to be clarified.

The total time spent to perform the test was significantly shorter in the conductivity test compared with the classic test (median of 45 vs. 50 minutes, respectively), not taking into consideration the time spent to conduct the measurement of sweat chloride in the classic test. At our health care facility, the measurement of sweat chloride is only performed once a week; therefore, the result of the test may take 1 to 7 days to be released after sweat collection, whereas the result of the conductivity test is immediate.

With regard to cost, the amount spent with the conductivity test was a little lower than that spent with the classic test, this being an additional advantage of this method, which may reduce the costs for the public and private health system at long term.

Due to the simplicity of the performance of the conductivity test, which does not require a highly trained professional exclusively devoted to that task, as well as the accuracy of the test, streamlined result and costs at least equivalent to those of the Gibson & Cooke technique, we recommend that the conductivity test is used by health care facilities that do not have professionals and a laboratory prepared to perform the classic test.

## Conclusions

Macroduct® sweat collection system, with sweat conductivity analysis, showed to be an easily performed, accurate method, including the possibility of analysis of sweat electrolytes even in small samples. In our population, it showed excellent sensitivity and specificity when compared with the classic test, as well as shorter performance time and lower cost.

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