Original Article

A new method of sweat testing: the CF Quantum® sweat test☆

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Abstract

Background: Conventional methods of sweat testing are time consuming and have many steps that can and do lead to errors. This study compares conventional sweat testing to a new quantitative method, the CF Quantum® (CFQT) sweat test. This study tests the diagnostic accuracy and analytic validity of the CFQT.

Methods: Previously diagnosed CF patients and patients who required a sweat test for clinical indications were invited to have the CFQT test performed. Both conventional sweat testing and the CFQT were performed bilaterally on the same day. Pairs of data from each test are plotted as a correlation graph and Bland–Altman plot. Sensitivity and specificity were calculated as well as the means and coefficient of variation by test and by extremity. After completing the study, subjects or their parents were asked for their preference of the CFQT and conventional sweat testing.

Results: The correlation coefficient between the CFQT and conventional sweat testing was 0.98 (95% confidence interval: 0.97–0.99). The sensitivity and specificity of the CFQT in diagnosing CF was 100% (95% confidence interval: 94–100%) and 96% (95% confidence interval: 89–99%), respectively. In one center in this three center multicenter study, there were higher sweat chloride values in patients with CF and also more tests that were invalid due to discrepant values between the two extremities. The percentage of invalid tests was higher in the CFQT method (16.5%) compared to conventional sweat testing (3.8%) (p b 0.001). In the post-test questionnaire, 88% of subjects/parents preferred the CFQT test.

Conclusions: The CFQT is a fast and simple method of quantitative sweat chloride determination. This technology requires further refinement to improve the analytic accuracy at higher sweat chloride values and to decrease the number of invalid tests.

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Keywords: Sweat testing; Newborn screening; Sensitivity; Specificity; Cystic fibrosis

1. Introduction

The approved methods for sweat testing are Gibson-Cooke Pilocarpine Iontophoresis (GCQPIT) or the Wescor Macroduct® Sweat Test system. There are many steps in these methods that can and do lead to errors [1]. The GCQPIT and Macroduct® methods can result in quantity not sufficient (QNS) sweat test samples exceeding 20% and thus, delays in diagnosis [2]. These methods are time intensive and for parents of infants with an abnormal newborn screening test for cystic fibrosis (CF), the parents may need to wait for 60–90 minutes or more for results of the sweat test. Therefore, there is a critical need to improve sweat testing technology.

The CF Quantum® Sweat Test System (CFQT) is the next generation evolution of the CF Indicator™ system originally manufactured by Medtronic, Inc., Minneapolis, Minnesota [3]. This test has three components: (1) a portable, wearable electrode

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and controller set to deliver pilocarpine to an extremity (Fig. 1); (2) a chloride test patch that collects the sweat (a visible chemical reaction occurs in the patch that results in a white precipitate in the center of the patch. The surface area of the white precipitate is directly proportional to the sweat chloride value. Fig. 2); and (3) an analyzer which scans the patch with a camera and calculates the sweat chloride value.

In this multicenter pilot study, we performed bilateral conventional sweat tests and bilateral CFQT tests in patients with a previous diagnosis of CF or CF related metabolic syndrome (CRMS [4]) and in patients who required a sweat test for clinical indications. Our primary objective was to compare the diagnostic accuracy and analytic validity of the CFQT to conventional sweat testing. Secondary objectives were to compare the quantity not sufficient (QNS) rates of the conventional and CFQT tests and to determine the subjects’/parents’ preference of test systems.

2. Methods

Results are reported as per the recommendations of the STARD (Standards for Reporting of Diagnostic Accuracy) initiative [5]. (STARD checklist and flow diagrams for analytic validity and diagnostic accuracy are available in the online supplement.) This study was completed at the University of Wisconsin, Madison, WI, the University of Minnesota, Minneapolis, MN and at the University of Utah, Salt Lake City, UT (clinicaltrials.gov identifier NCT01345617). Institutional review board approval was obtained at all three sites and all subjects or legal guardians signed consent forms prior to participation in the study. Patients with previously diagnosed CF or CRMS (n = 88) were invited to undergo a conventional sweat test and CFQT test during a routine clinic appointment. The first test to be performed, CFQT or conventional sweat testing, was randomly assigned in this group. We also invited patients to participate in the study who had a sweat test ordered by their provider (n = 82), either because of a clinical suspicion of CF or as part of follow-up of an abnormal CF newborn screening test. The subjects in this group had the conventional sweat test performed first and the CFQT test performed second. Each subject had a bilateral conventional sweat test performed and a bilateral CFQT test performed on the same day. The preferred site was the forearm. An area of the arm did not undergo pilocarpine iontophoresis or collection of sweat more than once. If there was inadequate space on the forearm for both tests, then the CFQT was performed on the thighs. Subjects were invited into the study based on investigator and research coordinator availability and subjects’ willingness to sign the consent form. Thus, patients were not studied consecutively.

Conventional sweat testing was performed per the standards of the Clinical and Laboratory Standards Institute (CLSI) [6]. Sweat testing at the University of Wisconsin was by GCQPIT with sweat collected on filter paper; sweat testing at the University of Utah was by GCQPIT with collection of sweat on gauze, and conventional sweat testing at the University of Minnesota was by the Wescor Macroduct® Sweat Test system. Pilocarpine iontophoresis occurred for 5 minutes and collection of sweat occurred for 30 minutes. All three sites used the same model of chloridometer: Labconco model 442-5000, Kansas City, Missouri. Additionally, all three sites participated in quality assurance through the College of American Pathologists.
sweat analysis survey. QNS results were defined as less than 75 mg of sweat per the GCQPIT method and less than 15 µL per the Wescor Macroduct® method. Sweat testing was performed bilaterally and the results were not averaged.

For the CFQT, pilocarpine iontophoresis occurred for 8 minutes (this was the approved administration time of iontophoresis for the CFQT controller and electrode set per the United States Food and Drug Administration (FDA)). The collection of sweat on the patch occurred until the sweat front (a red circle on the patch) reached a stop ring of 15 mm in diameter. In preclinical laboratory testing, this volume of sweat correlated with a sweat rate exceeding 1 g/M²/minute. The test was deemed QNS if the sweat front did not reach the stop ring by 20 minutes. The sweat collection time was recorded on the case report form. After obtaining an adequate amount of sweat, the patch was removed from the extremity and allowed to dry for a minimum of 15 minutes prior to being placed in the analyzer.

For both the conventional sweat tests and the CFQT, the test was considered invalid if the sweat chloride values from the two extremities were >15 mmol/L difference for sweat chlorides of >60 mmol/L and were considered invalid for a difference of >10 mmol/L for sweat chloride values of ≤60 mmol/L [6].

At the Universities of Wisconsin and Minnesota, the clinical laboratory technician performing the conventional sweat test also performed the CFQT test. At the University of Utah, staff from the clinical laboratory performed the conventional sweat test and a research nurse performed the CFQT test.

The interpretation of sweat test results was per the United States Cystic Fibrosis Foundation guidelines [7]. For infants less than 6 months of age, a sweat chloride of ≤29 mmol/L was normal, 30–59 mmol/L was intermediate, and ≥60 mmol/L was abnormal and consistent with CF. For subjects ≥6 months of age, a sweat chloride of ≤39 mmol/L was normal, 40–59 was intermediate, and ≥60 mmol/L was abnormal and consistent with CF. With bilateral sweat testing being performed, the interpretation of the results used the higher of the two sweat chloride values, as per the CLSI guidelines [6].

After the conventional sweat test and CFQT tests were performed, the subjects or their legal guardians completed a questionnaire in which they stated their preference for one of the tests (available in online supplement).

2.1. Statistical analysis

Conventional sweat test and CFQT test results were compared using a scatter plot of matching pairs from the same extremity. Individual data points were not graphed and compared if one or both tests were insufficient due to either QNS or technical difficulty or the test was invalid due to discrepant values from the two extremities. The Pearson correlation coefficient and corresponding 95% confidence intervals (CI) for the overall study and each participating site were calculated. A Bland–Altman analysis was conducted to examine the level of agreement between results obtained by the CFQT and conventional sweat testing [8]. Within-subject variability between tests was analyzed by calculating the coefficient of variation for paired samples. The 95% confidence intervals for the coefficient of variations were constructed using the nonparametric bootstrap method. Diagnostic outcomes of the CFQT and conventional sweat test were evaluated by calculating the Kappa statistic. Sensitivity and specificity of the index test (CFQT) compared to the reference test (GCQPIT/Macroduct®) were calculated with 95% CIs. The duration of sweat collection time between conventional sweat testing and CFQT was compared using a two-sample test. The proportions of QNS and invalid tests were compared between the conventional sweat tests and CFQT using a paired McNemar’s test. All p-values were two-sided and p-values <0.05 were considered statistically significant.

3. Results

The first subject to enter the study was in May 2012 and the last subject to complete the study was in September 2013. There were 57 subjects at the University of Wisconsin site (28 with a previously known diagnosis of CF or CRMS and 29 referred to the sweat testing laboratory); there were 56 subjects at the University of Minnesota site (28 with previously diagnosed CF or CRMS and 28 referred to the sweat testing laboratory), and there were 57 subjects at the University of Utah site (32 with a previous diagnosis of CF or CRMS and 25 referred to the sweat test laboratory). The characteristics of the subjects are shown in Table 1. Preliminary data have been presented at the European Cystic Fibrosis Conference [9] and the North American Cystic Fibrosis Conference [10].

Of the potential 340 bilateral conventional sweat tests, 4 tests were invalid (2 with discrepant sweat chloride values and 2 with sweat chloride values >160 mmol/L). Of the potential 340 bilateral CFQT tests, there were 40 that were unavailable for analysis (2 tests had analyzer technical error, 4 tests were invalid due to sweat chloride greater than 160 mmol/L [two of these were consistent with invalid GCQPIT results of >160 mmol/L], 15 tests had smearing of sweat on the patch [7 of these were sweat collections on the thigh], 18 tests

Table 1

<table>
<thead>
<tr>
<th>Characteristics of study subjects.</th>
<th>Known CF or CRMS</th>
<th>Referred for sweat test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number</td>
<td>88</td>
<td>82</td>
</tr>
<tr>
<td>Center 1</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td>Center 2</td>
<td>28</td>
<td>29</td>
</tr>
<tr>
<td>Center 3</td>
<td>32</td>
<td>25</td>
</tr>
<tr>
<td>Female gender — no. (%)</td>
<td>49 (56)</td>
<td>40 (49)</td>
</tr>
<tr>
<td>Center 1</td>
<td>14 (50)</td>
<td>14 (50)</td>
</tr>
<tr>
<td>Center 2</td>
<td>16 (57)</td>
<td>15 (52)</td>
</tr>
<tr>
<td>Center 3</td>
<td>19 (59)</td>
<td>11 (44)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD (yr)</td>
<td>12.6 ± 5.5</td>
<td>7.8 ± 13.2</td>
</tr>
<tr>
<td>Center 1</td>
<td>14.7 ± 5.3</td>
<td>5.5 ± 12.7</td>
</tr>
<tr>
<td>Center 2</td>
<td>12.1 ± 5.3</td>
<td>10.3 ± 12.6</td>
</tr>
<tr>
<td>Center 3</td>
<td>11.2 ± 5.5</td>
<td>7.3 ± 14.4</td>
</tr>
<tr>
<td>Range</td>
<td>1–29 yrs</td>
<td>12 days–66 yrs</td>
</tr>
<tr>
<td>Center 1</td>
<td>7–29 yrs</td>
<td>12 days–53 yrs</td>
</tr>
<tr>
<td>Center 2</td>
<td>1–20 yrs</td>
<td>15 days–49 yrs</td>
</tr>
<tr>
<td>Center 3</td>
<td>1–19 yrs</td>
<td>24 days–66 yrs</td>
</tr>
</tbody>
</table>
had discrepant sweat chloride value results and 1 subject refused the test on the second extremity).

The QNS rates were 2.6% for the conventional sweat test (9 of 340 tests, 95% CI: 1.2–5.0%) and 4.7% for the CFQT test (16 of 339 tests, 95% CI: 2.7–7.6%) (p = 0.046). When the conventional sweat test was QNS, there was also a QNS in the same subject for the CFQT in 8 of the 9 tests. For conventional sweat testing, QNS occurred in 2 subjects who were <6 months old and 4 subjects who were >6 months old. For the CFQT, QNS occurred in 3 subjects who were <6 months old and 9 subjects who were >6 months old. Of note is that of the 64 CFQT tests that were performed on thighs, 6 of these (9%) were QNS. There were 275 CFQT tests performed on the forearm with 10 tests (3.6%) resulting in QNS (p = 0.092).

The overall tests that were not available (QNS plus invalid tests) were 13 of 340 (3.8%; 95% CI: 2.2–6.4%) for conventional sweat testing and 56 of 339 (16.5%; 95% CI: 13.0–20.8%) for CFQT (p < 0.001). The unavailable test results by number of patients were 8 subjects by conventional sweat testing (2 subjects were <6 months of age and 6 subjects were >6 months of age) and 39 subjects by CFQT (12 subjects were <6 months of age and 27 subjects were >6 months of age). Most of these unavailable tests were one of the two bilateral tests. Thus, sweat test interpretation for at least one test was available for 154 of the 170 subjects (91%) (Fig. 2 of online supplement).

The average collection time of sweat in the CFQT test was 8.8 ± 3.6 minutes. This was significantly less (p < 0.001) than the standard 30 minute collection time for conventional sweat testing.

After accounting for QNS sweat tests and invalid tests/technical difficulties, there were 278 evaluable pairs of conventional sweat tests and CFQT available for analysis. The CFQT results plotted against the conventional sweat test results are in Fig. 3. The overall Pearson correlation coefficient was 0.98 (95% CI: 0.97–0.99). The correlation coefficient did not vary between centers (0.99 at centers 1 and 2 and 097 at center 3). Bland–Altman plot of the differences of the CFQT and conventional sweat test versus their averages is illustrated in Fig. 4.

The coefficient of variation between paired extremities values by test were CFQT: 5.5% (95% CI: 4.8–6.3%); Macrodust®: 4.5% (95% CI: 3.5–5.5%); filter paper: 4.3% (95% CI: 3.5–5.3%); and gauze: 3.8% (95% CI: 3.0–4.6%). The coefficient of variation values for all tests was well below 10%, indicating acceptable within-subject variability between tests.

There were 5 tests in 3 subjects (two previously known to have CF) in which the conventional sweat test results were intermediate but the CFQT results were in the definitively abnormal range. (Table 2 shows interpretation of test data per subject with CFQT as the index test and conventional sweat testing as the reference test.) In a 15 yr old with CF, sweat chloride results per the Macrodust® method were 55 and 54 mmol/L on the right and left arms, respectively, with CFQT results of 67 and 65 mmol/L on the right and left arms, respectively. In a 17 yr old with CF, sweat chloride results per GCQPIT were 54 and 55 mmol/L on the right and left arms, respectively, with CFQT results of 60 and 62 on the right and left arms, respectively. Lastly, in a 40 day old

referred to the laboratory due to an abnormal CF newborn screen, the GCQPIT result on the right arm was 59 mmol/L and the CFQT result on the right thigh was 62 mmol/L. Sweat smeared the patch on the left thigh, thus there were no available results for comparison on the left extremities. If we take a conservative approach and state that these CFQT results were false positives, then the CFQT sensitivity was 100% (95% CI: 94–100%) and the specificity was 96% (95% CI: 89–99%). The Kappa statistic was 96% (95% CI: 92–100%) indicating an excellent level of agreement between the CFQT and conventional sweat test results.

The conventional sweat testing procedures did not result in any adverse events. In the CFQT tests, there was one subject who had redness at the site of the pilocarpine iontophoresis that lasted for several days and then self-resolved. In the post-test questionnaire, 88% of subjects/parents preferred the CFQT test.

4. Discussion

This pilot study has demonstrated that the CFQT provides a quantitative measure of sweat chloride values and yields results that reliably distinguishes normal (non-CF) subjects from persons with CF. This technology is easy to perform, yields results more quickly than traditional sweat testing and is preferred by patients or their parents over traditional sweat testing.

Although one can establish a diagnosis of cystic fibrosis based on identifying two mutations, there are many mutations that are of unknown consequence. This may be resolved some day by the CFTR2 project [11], but currently, the vast majority of mutations have not been definitively characterized. Additionally, the number of mutations that are on either newborn screening panels or are available from commercial laboratories varies. Guidelines from both the United States CF Foundation [7] and the European Cystic Fibrosis Society [12] state that the sweat test remains as the diagnostic test of choice to rule in or rule out CF. Another advantage of the sweat test, compared to genetic testing, is that results are available on the same day of the test.

The original description of the sweat test was by Gibson and Cooke in 1959 [13] and this technique has not appreciably changed in the last 60 yrs. After stimulation of sweat glands by iontophoresis of pilocarpine, sweat is collected on gauze or filter paper. In the original 1959 description of the procedure, sweat chloride analysis was by the polarographic method of Zimmerman and Layton [14]. This utilized a reaction between mercury and chloride in solution, and the measurement of current at a fixed applied voltage was directly proportional to the chloride concentration. (An alternative method of measuring chloride is the Schales and Schales [15] titrimetric method in which titration of the sweat sample with mercuric nitrate and an indicator solution of s-diphenylcarbazone was performed until an end point was reached of a pale violet color.) Chloride determination later evolved to the coulometric titration method of Cotlove [16]. This utilizes the principle of silver ions generated from a silver anode combining with the chloride to result in silver-chloride. A current is passed through the liquid and as silver-chloride is formed, the current decreases which
results in an increased generation of silver ions to bring the silver concentration back to its original level prior to the chloride induced precipitation. This process of generating fresh silver ions continues until all the chloride is precipitated. The concentration of chloride in the original solution is then determined by measuring the length of time during which the silver-generating current flowed.

An alternative method of sweat collection is by the Macroduct® method [17,18] in which sweat is collected in microbore tubing. For both the GCQPIT and Macroduct® methods, there are many steps of pipetting reagents in order to prepare the sweat sample for analysis in the chloridometer. (There is a new FDA approved chloridometer, the Elitech Chlorochek® Chloridometer®, that can accept a 10 μL sample of sweat directly from the microbore tubing.) Thus, there many steps in the sweat testing procedure in which errors can occur.

The three components of the CFQT yield a faster and simpler procedure of quantitative sweat testing. The controller and electrode set is a wearable device for iontophoresis of pilocarpine into the skin. This uses a pilocarpine interface gel similar to the pilogel that is used in the Macroduct® system. Unlike the Macroduct® and GCQPIT methods in which the patient is attached by wires to an external “box” that contains batteries, the CFQT iontophoresis device is worn on an extremity and the patient is not tethered to an external battery-containing box (Fig. 1). The second component of the CFQT is the chloride test patch. This contains a solution of silver nitrate, a second solution of phenol red and potassium chromate. As the sweat sample enters the fill port and migrates to the front of the chloride test patch, it picks up the phenol red and creates a dark red ring, which indicates the amount of sweat that has been collected in the sample. When the chloride ions in the sweat sample come into contact with the silver chromate of the chloride test patch, an ion exchange reaction occurs. This ion exchange creates silver chloride, an insoluble white precipitate formed in the center of the patch. The third component of the CFQT is the analyzer which uses a camera and computer software to result in a sweat chloride value.

As can be seen in the Bland–Altman plot (Fig. 4), the correlation between the CFQT and conventional sweat testing was best at sweat chloride values of <80 mmol/L, with all of the values within ±1.96 SD. There was more variation in sweat chloride values above 80 mmol/L, particularly in center 3. This site received a patch lot that was manufactured at a different
time and that was not used at the other two centers. Although the higher sweat chloride values in CFQT compared to GCQPIT in this center still yields a diagnosis of CF, the analytical accuracy is not as good as desired. The manufacturer of the CFQT recognizes that the production of the patches needs to improve and that this lot-to-lot variability needs to be eliminated. Similarly, the invalid tests in the CFQT due to discrepancy in the bilateral values of sweat chloride occurred exclusively in CF patients whose sweat chloride values are in the higher range compared to normal subjects. There were 3 subjects at center 1, 1 subject at center 2, and 5 subjects at center 3 who had invalid CFQT tests due to discrepant bilateral sweat chloride values.

Despite the variability seen in the Bland–Altman plot, the sensitivity and specificity of the CFQT is excellent. In the results section of this paper, we used a conservative approach of a specificity of 96% due to 5 tests in 3 subjects in which the conventional sweat test results were intermediate but the CFQT results were in the definitively abnormal range. In fact, two of these subjects had a previous diagnosis of CF and the other subject was a 40 day old with a positive newborn screen and who was initially diagnosed with CRMS (F508del/I506L) based on the GCQPIT result. A repeat GCQPIT at 5 months of age had a definitively elevated sweat chloride values and this baby’s diagnosis was changed to CF. Therefore, one would be justified in stating that these were not false positive tests and that the specificity of the CFQT is also 100%.

Another advantage of the CFQT system is that the collection of sweat is much more rapid than conventional sweat testing and thus the results are more quickly available (as soon as 15 minutes after the patch is removed). This aspect of this new technology is particularly desirable in the arena of newborn

Table 2
GCQPIT/Macroduct versus CFQT results.

<table>
<thead>
<tr>
<th>GCQPIT/Macroduct true diagnosis</th>
<th>CFQT results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CF</td>
</tr>
<tr>
<td></td>
<td>N (%)</td>
</tr>
<tr>
<td>Positive</td>
<td>72 (100%)</td>
</tr>
<tr>
<td>Negative</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Total</td>
<td>72</td>
</tr>
</tbody>
</table>

Fig. 4. Bland–Altman plot of differences between CFQT and conventional sweat chloride versus their average. Solid line, mean difference; dotted lines, mean difference ± 1.96 SD.
screening. Some laboratories will perform sweat collection in the morning, but will not analyze sweat until the afternoon. Previous research has shown that this delay in presenting sweat test results to parents of infants with a positive newborn screen can lead to misinformation and lingering concerns about CF in their child [19].

A drawback of the CFQT is that in this pilot study, the percentage of CFQT tests unavailable for analysis (16.5%) far exceeded the percentage of conventional sweat tests unavailable for analysis (3.8%). The reasons for CFQT tests being unavailable for analysis were technical errors, smearing of the patches and invalid tests due to discrepant bilateral sweat chloride values. Given that this was a pilot study of a new technology, it is not surprising that there would be technical issues with the equipment. With regard to the smearing of sweat on the patches, there is a learning curve for technicians to undergo and we have learned of a specific method in removing the patches to prevent this smearing. Lastly, as discussed previously, center 3 contributed the majority of discrepant sweat chloride values due to their unique patch lot that yielded higher sweat chloride values in CF patients.

Prior to beginning this study, we expected a lower QNS rate with CFQT compared to conventional sweat testing. However, there was no significant difference in the QNS rate of the CFQT compared to conventional sweat testing. Of note is that the protocol specified that for subjects who required a sweat test on clinical grounds, the conventional sweat test was performed first on the forearm. If there was inadequate space on the forearm to also perform the CFQT test, then that test was completed on the thigh. In comparing QNS rates of the CFQT on the forearm compared to the thigh, there was a lower rate on the forearm. In our personal experience with conventional sweat testing, we have found that it is more challenging to obtain a sufficient quantity of sweat from thighs compared to forearms. A larger study that includes more infants would be important to determine if this new technology yields a lower QNS rate, an issue that is of high concern in newborn screening programs [20]. Similarly, a larger study is required to establish that this new method of quantitative sweat chloride determination is equivalent to the previously established gold standard of GCQ PIT or Macroduct® [21].

In summary, the CFQT yields reliable sweat test results and can distinguish patients with CF from normal subjects. The test procedure is much faster than conventional sweat testing and thus parents or patients can receive results in a timely fashion. Further refinement of manufacturing processes of the patches should yield results that show less variation.

Conflict of interest statement

None of the authors have any personal or any financial relationships that would constitute a conflict of interest.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jcf.2014.05.001.

References


