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Feasibility and normal values of an integrated conductivity (Nanoduct™) sweat test system in healthy newborns

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Keywords: Sweat test; Conductivity; Cystic fibrosis; Newborn screening

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ABSTRACT

Background: Nanoduct™is a simple and practical sweat analysis system measuring conductivity in situ. It requires only three microlitres of sweat, making it especially applicable to newborns.

Methods: We measured conductivity in 260 healthy term infants at the age of four days, and again at four weeks to determine the proportion of successful tests, test duration, and normal values for sweat conductivity in newborns.

Results: Sufficient sweat was collected in 159/260 of four-day olds (61%), and in 225/239 of four-week olds (94%). Mean (sd) test duration was 27 (5) and 25 (5) min. Mean (sd, range) conductivity was 53 mmol/l (16, 8–114) at age four days, and 36 (9, 12–64) at four weeks.

Conclusions: Determination of sweat conductivity using Nanoduct™ cannot be recommended for four-day old newborns. However, at the age of four weeks the success rate is high (94%), and conductivity values at that age are comparable to older healthy children.

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INTRODUCTION

The sweat test is a key component for establishing a diagnosis of cystic fibrosis (CF) in infants with a positive result in newborn screening (NBS) [1,2]. Collecting sufficient sweat for analysis is a challenge in small infants and some guidelines recommend delaying the test until the infant is more than two weeks of age or weighs more than 3 kg [3-5]. Although for infants below three months of age test failure rates of up to 40% have been reported [6-10], North American recommendations aim for a failure rate of 10% or less for sweat tests in NBS programs [2,6].

Since the invention of the sweat test based on the pad method by Gibson and Cooke 60 years ago [11,12], sweat testing has evolved. The nowadays widely accepted Macroduct™ collection system needs 15 µl of sweat to analyze chloride concentration [2-4], while the sweat flow sensor of the Nanoduct™ sweat test system requires only 3 µl. This makes it especially applicable to newborns. However, it does only measure conductivity [13].

Studies using Nanoduct™discriminated well between children with and without CF [13-17]. This is also true for other sweat tests that measure conductivity instead of chloride concentration, for instance the Sweat-Check™ [18-22]. Despite this, the European practice guidelines for neonatal screening and the US guidelines for diagnosis of CF do not recommend measuring sweat conductivity to diagnose CF [1,2].

This study assessed the feasibility of sweat testing with the Nanoduct™ system in healthy newborns at the age of four days and four weeks, by determining the duration of the tests and the proportion of tests that were successful. We also wanted to determine the normal values of sweat conductivity for Nanoduct™ in this age group.

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METHODS

Subject and study design

We conducted this single-center study from June 2013 to December 2014 with 260 healthy term infants born in the maternity unit of the Department of Gynaecology at the Cantonal Hospital St. Gallen in Switzerland. Each infant was tested twice with the Nanoduct™ (Wescor, Utah, USA) sweat system, at age 3–4 days and 3–4 weeks. We chose these age groups because in Switzerland NBS with the Guthrie test is performed at the age of 3–4 days, before infants leave the birth clinic [23,24]. When they are 3–4 weeks old, children with a positive NBS result are recalled to a CF center for sweat testing. We asked all parents of healthy infants born in the hospital during this period to participate, except those whose infants were born prematurely (gestational age b37 weeks), had a birth weight below 3000 g, or were sick, presenting symptoms such as oedema, hyperbilirubinemia, signs of dysmaturity, malnourishment, or a systemic disease. We also excluded children whose parents did not speak German, and all those who were discharged on a weekend.

Nanoduct™ sweat test analysis system

The Nanoduct™ sweat test is a micro-flow conductometric device, which induces and analyzes the conductivity of sweat in situ while attached to a patient. The procedure is described in detail elsewhere [13,20]. In brief, iontopheresis using small Pilogel™ iontophoretic discs and direct current supplied by the Nanoduct™ inducer/analyzer is followed by a continuous-flow analysis of sweat conductivity using a conductivity sensor. The continuous-flow principle allows display of the initial sweat rate in grams per square meter of skin surface per minute, which is important in accepting sweat test results (valid results: ≥1 g/m2/min). Its continuous sweat flow sensor requires only 3 µl of sweat. The value of conductivity is expressed as mmol/l eq NaCl. This is not equal to a quantitative chloride measurement; its displayed equivalent is approximately 20 mmol/l higher than the sweat chloride concentration because of additional anions such as lactate and bicarbonate [18,19,21].

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The sweat tests at the age of four days were carried out in the Department of Gynaecology of the Cantonal Hospital St. Gallen by two trained and experienced persons (Agnieszka Mazur and a research nurse). The sweat tests at the age of four weeks were performed at infants' homes or in the Children's Hospital in St. Gallen by the same two persons. The Nanoduct™ device was placed on a forearm or a leg. The sweat test was considered valid (that is, a successful test) if the sweat rate was ≥1 g/m2/min, and as not valid if the sweat rate was lower (b1 g/m2/min) or zero (no sweat rate displayed on Nanoduct™).

The parents were told by the technician that the test results needed to be interpreted by the doctor, and were then informed by the investigator after the end of the two tests only if the result was regarded as ambiguous or not normal. If the second sweat test at the age of 4 weeks was above an upper limit of 60 mmol/l, we offered the parents another sweat test at the Children's Hospital, followed by a chloride measurement using the Macroduct™ method, if the conductivity value was still elevated.

Statistical analysis

We calculated the proportion of successful tests as the number of tests with valid results divided by the total number of tests performed. We compared the proportion of successful tests across quintiles of body weight at the day of the test, and across quintiles of weight loss between birth and the test day, in percent of birth weight, using tests for trend to assess statistical significance. We checked the distribution of quantitative data (duration of tests, conductivity) using histograms, Q–Q plots, and Shapiro–Wilk and Shapiro–Francia tests for normality. Since data were normally distributed, we described sweat conductivity (mmol/l) and test duration (minutes) as mean values and standard deviations (sd), and determined 95% (99%) reference intervals for sweat conductivity as the mean ± 2 (± 3) standard deviations. For infants with paired data, we compared agreement with a Bland Altman plot, displaying the mean of the two values on the x axis versus the difference between the two

measurements on the y axis.We analyzed the data using STATA version 13.1 (StataCorp. 2005. Stata Statistical Software: Release 13.1 StataCorp LP, College Station, TX, USA).

RESULTS

Between July 1, 2013 and Dec 31, 2014, 2231 infants were born in the maternity unit in St. Gallen. Of these, 366 were excluded because of preterm birth, 707 because of low birth weight and 898 for different reasons (discharge at weekends, parent's insufficient knowledge of the German, clinical symptoms such as hyperbilirubinemia, or no parental consent). None of the children born in this unit had a positive CF-NBS result . Parents of 260 newborns agreed to participate (Table 1). In total, 239 infants had two sweat tests (Table 2). Twenty-one infants were lost to follow-up at four weeks, twelve due to parental refusal, six due to no answer to repeated phone calls, and three because of unavailability of the sweat test equipment on the test day. The time needed to perform the sweat test was on average 27 min (5–40, sd 5 min) at the age of 4 days, and 25 min (14–40, sd 5 min) at the age of 4 weeks.

The proportion of successfully conducted sweat tests was 61% at age 4 days, and 94% in four-week olds (Table 2). At age four days, 159 of 260 infants (61%) produced enough sweat (≥3 μl), while 23 (9%) had an insufficient quantity and 78 (30%) produced no sweat at all (Table 2). The proportion of successful tests was positively associated with body weight, varying from 49% for those in the lowest quintile (2.8–2.9 kg) to 69% in those in the highest (3.7–4.6 kg, $p = 0.024$). The proportion of successful tests was also associated with weight loss: it was lowest (48%) in those infants who had lost most weight between birth and the day of measurement ($p = 0.034$). At age four weeks, 225 of 239 infants (94%) produced sufficient sweat. Five children (2%) had insufficient quantities and nine (4%) had no sweat. At this age, the proportion of successful tests was >90% across all quintiles of body weight, with no clear trend ($p = 0.221$).

At four weeks of age the sweat conductivity values were normally distributed (Table 3 and Fig. 1). The mean value was 35 mmol/l (range 12–64) and the upper limit of the 95% reference interval (mean +

1.96 sd) was 53 mmol/l. Two children (2%) had a conductivity value above the threshold of 60 mmol/l, and were invited for another sweat test at the Children's Hospital; one mother refused to come and the other child had a normal sweat test. The Bland Altman plot illustrates that the 2nd measurements were in average 18 mmol/l lower, with outliers at the two extremes, reflecting measurements that were technically unsatisfactory at one of the two time points (online Fig. 1).

DISCUSSION

This is the first study to generate normal reference values for conductivity using the Nanoduct™ sweat test in an unselected group of healthy newborns. Its main strength is the relatively large and homogeneous population of healthy newborns and their young age. The study included only children who cleared the CF-NBS program as healthy, non-CF children, but because we did no genetic testing in these children we cannot exclude the possibility that some children were healthy CF-carriers or had mild ('atypical') forms of CF [23]. Based on an incidence of CF in Switzerland of about 1 in 3000 [23,24], we expect that our study population could include about five CF carriers. Yet even if conductivity were slightly higher in carriers, this low number would not have strongly influenced our results. All sweat tests were performed strictly according to guidelines, with the same equipment, by two trained testers in a single center, which minimizes the probability of differences in test results caused by variations in material or procedures. However, the very fact that this was a carefully conducted, single-center study that excluded low birth weight and sick infants might reduce the generalizability of the results. Although we included twice as many data points than generally requested as minimum number to determine reference values (120) [25], a larger sample would have been even more informative.

We are aware of only six other studies that have investigated the performance of the Nanoduct™ sweat test system and reported values in the normal range for conductivity (Table 4). None of the studies included children who could be considered totally healthy or normal: four analyzed data of patients with chronic respiratory symptoms referred to outpatient clinics for exclusion of CF [13-15,26], and two reported on sweat tests in neonates with a positive NBS result [16,17]. Still, our conductivity

results for healthy four-week old infants are comparable with these studies of older infants, children, and adults, which all reported mean values between 30 and 42 mmol/l. When comparing our results with reference values for sweat chloride in 5–6 week-old infants using the Macroduct™ collection system (median 12 mmol/l (IQR 9–15) [27], our equivalent conductivity values at four weeks (median 35 mmol/l, IQR 30–41) are on average 23 mmol/l higher (exactly the same value which was found by Mastella et al. [21] in his healthy control group), but the distribution approximated a normal distribution in both studies.

The proportion of successfully conducted sweat tests in our study was low (61%) at age 4 days, but excellent (94%) in four-week old. This is comparable to our previous multicenterstudy, where it was 48% in newborns (55% in term, 31% in preterm), 90% in older infants, and 95% in children and adults [14]. Our results also confirm earlier studies focusing on the Macroduct™sweat test, which reported lower proportions of successful tests in very young infants. For example, the Massachusetts NBS program found that the percentage of sweat tests interpreted as "quantity not sufficient" (QNS) was 17% at the age of 2 weeks, 12% at 3 weeks, 8% at 4 weeks, and 5% at 5 weeks [10].

In studies that have compared the Macroduct™directly with the Nanoduct™, Nanoduct™ usually performed better. For example, the Vernooij-van Langen et al. study reported a difference in QNS rates of 7% for Nanoduct™ tests, and 22% for Macroduct™ tests ($p = 0.002$) [17], while the Barben et al. study reported QNS results of 3% for Nanoduct™ tests and 15% for Macroduct tests ($p = 0.003$) [13].

What do these results mean? The current guidelines for CF-NBS in Europe and the guidelines for CF diagnosis in all age groups do not recommend conductivity measurements for the diagnosis of CF in newborns [1,2]. Our data suggest that at an age of four weeks, if not before, the Nanoduct™ sweat test method could be a useful tool for diagnosing CF in NBS programs, using 50 mmol/l as an upper limit, the threshold recommended by the CFF for performing confirmatory sweat chloride measurements [4]. Twelve of the 225 children in our study (5%) had a conductivity above the threshold of 50 mmol/l, and 2 (2%) above 60 mmol/l, the suggested upper normal value by the manufacturer [13].

In CF-NBS programs, a definite diagnosis should be made as quickly as possible to reduce parental anxiety [28]. We believe that Nanoduct™ is a good tool for excluding CF at the age of 3–4 weeks, as the success rate is high and the results are available within half an hour. In contrast, chloride measurements need hours to get a result, and the collection in newborns is challenging due to the higher quantity of sweat (15 µl), and thus high failure rates infants [6-9]. In Switzerland, children with a positive CF-NBS result are recalled for a sweat test at the age of 3–4 weeks. The failure rate of the Nanoduct™ at this age (6%) is acceptable according to the current recommendations, which aim for less than 10% [3-6]. Within the Swiss CF-NBS program, we use the Nanoduct™ and the Macroduct™ test in parallel since 2011, to reduce delays for parents of infants where theMacroduct™is not successful [13,14,17]. The Nanoduct™test system has the potential disadvantage that parents can spot the results, because conductivity is displayed on the screen of the apparatus attached to the child. Our lab technicians do not report any result. Parents who ask the lab technician are told that the data quality needs to be checked by the physician before results can be interpreted. In clinical routine in the Swiss neonatal screening, a CF specialist is called as soon as the Nanoduct™result is available and informs the parents.

This study is the first to provide normal ranges for sweat conductivity using the Nanoduct™ sweat test system for healthy newborns. Determination of sweat conductivity using Nanoduct™ cannot be recommended for four-day old newborns. However, at the age of four weeks the success rate is high (94%), and conductivity values at that age are comparable to those reported for older healthy children. The generated reference range improves the available evidence on the validity of this method. This suggests that Nanoduct™ might be a suitable sweat test for NBS programs in which children are seen in the first months of life.

Part of this work has been presented at the European Cystic Fibrosis Conference in Brussels, Belgium, June 10–13, 2015.

CONFLICT OF INTEREST

There is no conflict of interest. The study was sponsored by the Lung League of Canton St. Gallen, Switzerland, and the pulmonology funds of the Children's Hospital of Eastern Switzerland.

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TABLES

Table 1

Characteristics of the study population, and duration of the Nanoduct™ sweat test in newborns at the age of four days and four weeks (N = 260). [a]Measurement available for 259 out of 260 infants.

	Mean	sd	Range
Baseline (n = 260)			
Birth weight (g)	3519	381	3000–4845
Gestational age (weeks)	40.9	1.1	36.3–42.1
First measurement (at age 4 days, n = 260)			
Weight (g) [a]	3346	363	2780–4600
Age (days) [a]	4	2	2–8
Test duration (min)	27	5	15–40
Second measurement (at age 4 weeks, n = 239)			
Weight (g)	4184	492	3200–5500
Age (days)	27	5	19–64
Test duration (min)	25	5	14–40

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298 **Table 2**

299 Proportion of successfully completed Nanoduct™ tests (success rate) in healthy infants at the age of four days and four weeks. Abbreviations: CI, confidence

300 interval; n, number of children; n/a, not applicable. [a] Values in quintiles overlap due to rounding.

	Age 4 days (N = 260)					Age 4 weeks (N = 239)				
	Weight	n	%	95% CI	p-Value	Weight	n	%	95% CI	p-Value
All children		159	61	55–67			225	94	91–97	
By quintiles of weight [a]					0.024					0.221
	2.8–2.9	26	49	36–62		3.2–3.7	45	94	82–98	
	3.0–3.2	30	57	44–70		3.8–4.0	50	91	78–96	
	3.2–3.4	33	66	52–78		4.0–4.3	39	91	77–97	
	3.4–3.6	34	65	51–77		4.3–4.6	47	100	n/a	
	3.7–4.6	36	69	55–80		4.6–5.5	44	96	84–99	
By weight loss (in % birth weight)					0.034					
	−7.9–2.9	34	65	51–77						
	3.0–4.5	37	73	59–83						
	4.6–5.8	31	60	46–72						
	5.9–7.1	32	62	48–74						
	7.2–13	25	48	35–62						

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303 **Table 3**

304 Normal values of sweat conductivity (mmol/l) in healthy infants at the age of four days and four weeks

Age	Mean	sd	Range	95% reference interval	99% reference interval	Percentiles								
						1%	5%	10%	25%	50%	75%	90%	95%	99%
4 days	53	16	8–114	22–84	7–100	17	31	36	44	53	62	72	81	98
4 weeks	35	9	12–64	19–53	10–61	17	22	26	30	35	41	46	51	59

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307 **Table 4**

308 Results of studies looking at success rate and conductivity of the Nanoduct™ sweat test

Authors, journal, year of publication	Ref.	N	Age	Country	Inclusion criteria	Success rate	Mean conductivity for participants without CF mmol/l (sd, range)
Studies including children with respiratory symptoms							
Barben et al., J Pediatr, 2005	[13]	111	3 weeks–60 yrs. (median: 1.3 yrs.)	Switzerland	90 outpatients with pulmonary symptoms, 21 with CF	97%	36 (9, 17–59)
Losty et al., Ann Clin Biochem, 2006	[15]	100	14 days–56 yrs. (median in healthy: 1.1 yrs.)	Wales	Patients requiring sweat tests (58 healthy, 36 CF, 6 nonclassic CF)	97%	39 (median) (range 15–62)
Desax et al., Eur J Pediatr, 2008	[14]	1041	1 day–60 yrs.	Switzerland	Patients requiring sweat test, including 66 newborns (term and preterm), 237 infants, 690 children, 48 adults >16 yrs.	94% (overall) 48% (newborns) 90% (infants) 95% (children)	Overall: 37 (2–108) Infants: 51 (35–76)
Sezer et al., J Clin Med Res, 2013	[26]	2664	7 days–17 yrs. (median: 17 months)	Turkey	Patients requiring sweat test, including 366 infants <6 months	NA	Infants <6 months: 35 (14, 12–131)
Studies including children with a positive NBS result							
Sands et al., Folia Histochem Cytobiol, 2010	[16]	528	4–8 weeks	Poland	Infants with a positive NBS result (480 healthy, 42 CF, 6 inconclusive)	NA	30 (8, 17–57)
Vernooij-van Langen et al., Eur J Pediatr, 2015	[17]	108	12–90 days (mean: 30 days)	Netherlands	Infants with a positive NBS result (84 healthy, 17 CF, 7 inconclusive)	93%	42 (11, 26–83)
Studies including healthy newborns							
Kuehni et al. (this study)	NA	260 239	4 days 4 weeks	Switzerland	Healthy infants from maternity clinic	61% 94%	53 (16, 8–114) 35 (9, 12–64)

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FIGURES

Figure 1

Distribution of normal conductivity values (histogram) at the age of four days and four weeks.

a. Sweat test four days after birth: normal values (mean ± 2 sd) indicated by red bar b. Sweat test four weeks after birth: normal values (mean ± 2 sd) indicated by red bar