Measurement of whole unstimulated salivary flow in the diagnosis of Sjögren's syndrome

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Abstract

The criteria for a clinical diagnosis of Sjögren's syndrome remain controversial and vary widely from study to study. With respect to the oral component it is considered necessary to use some form of objective test, but many of those available are not suitable for use in a busy clinical situation. The purpose of this study was to evaluate a simple method for measuring the whole unstimulated salivary flow. Twenty five patients with Sjögren's syndrome, 69 young control subjects, 20 age matched normal older control subjects and 20 patients with rheumatoid arthritis without Sjögren's syndrome had their salivary flows measured. Whole unstimulated salivary flows in the young control subjects were higher than in all other groups. Patients with primary Sjögren's syndrome had lower flows than either the older controls or the rheumatoid patients. Among the patients with Sjögren's syndrome 52% had a flow of 0·1 ml/min or less compared with only 8% of age matched controls. The positive predictive value of this low flow was 81%. It is concluded that whole unstimulated salivary flows of 0·1 ml/min or less are highly specific for xerostomia. When interpreted in the context of all the clinical findings whole unstimulated salivary flows are useful for diagnosing the oral component of Sjögren's syndrome.

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The criteria for a clinical diagnosis of Sjögren's syndrome remain controversial and vary widely from study to study.[1] Some workers maintain that the diagnosis can only be made on the basis of objective tests[2] whereas others also accept subjective symptoms.[3] The former approach has the advantage, often required in research projects, of objectivity but it is inflexible and if a test fails or is refused a diagnosis cannot be made. The latter approach is more applicable to the real clinical situation but has the disadvantage that symptoms may be due to causes other than Sjögren's syndrome.

For a diagnosis of the oral component of Sjögren's syndrome it is therefore considered necessary to use some form of objective test.[4 5] Many have been proposed, including sialography, scintigraphy, taking salivary gland biopsy samples, and measurement of salivary flows. Some of these are difficult to perform or require special equipment and may not be suitable for everyday use in a busy rheumatology clinic. Probably the most straightforward test is the determination of salivary flow. Many workers measure the stimulated parotid flow[6–8] but this may not correlate with xerostomia and may be normal when basal secretion is reduced.[8] Stimulated parotid flows can also be difficult to obtain and patients may not tolerate the cannula or stimulus. Another major disadvantage is that a variety of stimulants is used, resulting in lack of agreement on the value for an abnormal result and making it impossible to compare data between studies.

Whole unstimulated salivary flow is probably more closely associated with xerostomia because it reflects the basal flow which takes place during most of the day.[8] It also measures the total contribution from all the glands. Whole flows are easy to measure, are reproducible, and the values should be comparable between centres and between different measurements in individual patients.

The purpose of this study was to evaluate a simple method for measuring whole unstimulated salivary flows and to establish the sensitivity, specificity, and predictive values of a positive (abnormal) result.

Materials and methods

A total of 134 subjects took part in this study (table 1). There were 25 patients with Sjögren's syndrome (table 2), eight of whom had primary Sjögren's syndrome with positive results for keratoconjunctivitis sicca (Schirmer's test and rose bengal staining) and xerostomia. In six patients xerostomia was confirmed by a positive labial gland biopsy sample (one or more foci of lymphocytes per 4 mm^2 of gland), but one patient refused biopsy and another had no focal infiltrates. In these two patients, however, the stimulated parotid flow was low enough (<0·5 ml/min) to establish the diagnosis.[5–7] Seventeen patients had secondary Sjögren's syndrome with rheumatoid arthritis and all had a dry mouth. In eight patients the oral component was confirmed on the basis of a positive result on a labial gland biopsy sample. In a further three patients a low parotid flow was considered consistent with the diagnosis. In the remaining six patients the oral component could not be confirmed, but

Table 1 Characteristics of patient groups

	Age (years)		*Mean (SD) whole unstimulated salivary flow (ml/min)*
	Range	*Mean (SD)*	
Sjögren's syndrome			
Primary (n=8)	34–68	52 (11·6)	0·10 (0·1)
Secondary (n=17)	44–68	56 (7·9)	0·22 (0·2)
Rheumatoid arthritis (n=20)	39–85	65 (11·8)	0·27 (0·1)
Older controls (n=20)	36–81	53 (11·4)	0·30 (0·3)
Younger controls (n=69)	18–31	21 (2·7)	0·53 (0·3)

Table 2 Characteristics of patients with Sjögren's syndrome. Mean (SD) age 55 (9·1) years

Patient no	*Age (years)*	*Sex*	*Focus score*	*Whole unstimulated salivary flow (ml/min)†*
Primary Sjögren's syndrome				
1	68	M	1	0
2	60	F	—	0·03
3	58	F	12	0·10
4	41	F	5	0·10
5	43	F	3	0·03
6	54	F	1	0·20
7	34	M	0	0·30
8	60	F	5	0
Secondary Sjögren's syndrome				
9	46	F	0	0·20
10	55	F	2	0·30
11	64	F	3	0·40
12	55	F	4	0·05
13	65	F	2	0·04
14	59	F	—*	0·50
15	68	F	0	0·50
16	49	F	0	0·01
17	50	F	3	0·12
18	68	F	0	0·10
19	56	F	4	0·15
20	45	F	0	0·25
21	44	F	6	0·07
22	59	F	3	0·10
23	49	F	0	0·07
24	61	F	0	0·60
25	60	F	—*	0·20

*Refused to have biopsy sample taken.
†Mean (SD) for primary Sjögren's syndrome, 0·095 (0·1); mean (SD) for secondary Sjögren's syndrome, 0·22 (0·2).

objective tests (Schirmer's test and rose bengal staining) were positive for keratoconjunctivitis sicca. A total of 14 of the 25 patients with Sjögren's syndrome had a positive result on a labial gland biopsy sample and this subset was considered as a separate group for some of the analyses.

There were three control groups (table 1). The first consisted of 69 young healthy volunteers (39 women, 30 men; mean (SD) age 21 (2·7) years), none of whom had any history of rheumatoid arthritis, autoimmune disease, dry mouth, nor treatment with drugs. The second group consisted of 20 older volunteers approximately matched to the Sjögren's syndrome group (12 women, eight men; mean (SD) age 53·3 (11·4) years). None had rheumatoid arthritis, autoimmune disease; any history or evidence of Sjögren's syndrome, nor any history of treatment with drugs. The third control group consisted of 20 patients with classical or definite rheumatoid arthritis[9] (all women; mean (SD) age 65 (11·8) years). None had any evidence either clinically or serologically of Sjögren's syndrome. None showed any signs or symptoms of dry eyes or dry mouth and Schirmer's test was negative in all subjects (>10 mm wetting of paper).

MEASUREMENT OF FLOWS

All subjects had their whole unstimulated salivary flows measured mid morning, at least one to two hours after the last food intake. The subject was asked to sit in a relaxed and upright position and to allow all saliva to drain into a beaker by drooling or gentle spitting. They were instructed not to masticate, swallow, or speak. Saliva was collected for a period of 15 minutes, allowed to settle, and then measured in a graduated syringe. The flow was expressed in ml/min.

Thirteen of the patients with Sjögren's syndrome also had their stimulated parotid flows measured. This was carried out at a separate visit and had initially been our method of choice. Stimulated parotid flows were measured by applying a Lashley cannula over the duct of one parotid gland with gentle suction from a syringe. The stimulus was a drop of lemon juice applied to the tongue about once a minute throughout a 10 minute collection period. Salivary flow was expressed as ml/min/gland.

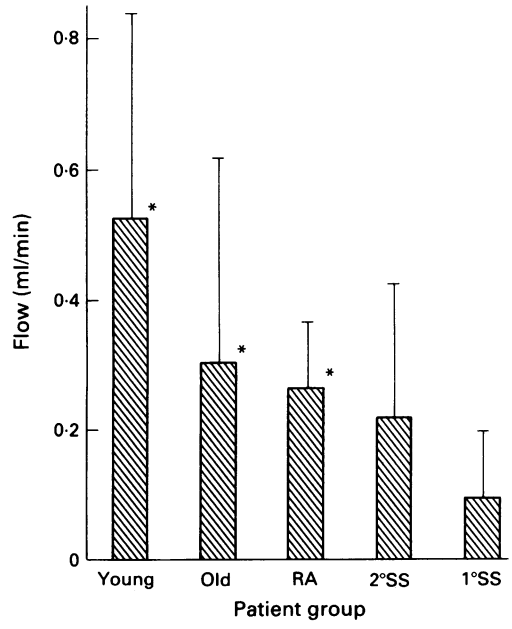
The 69 subjects in the young control group also had their whole stimulated salivary flow measured. Saliva was collected by spitting for 10 minutes while chewing on a block of paraffin wax.

STATISTICAL ANALYSIS

Comparisons between groups were performed using a Mann Whitney U test and correlations between parameters were tested by regression analysis. Specificity, sensitivity, and predictive values were calculated using standard methods described by Miller.[10]

Results

The results are summarised in tables 1 and 2 and the figure. There was great variability in the whole unstimulated salivary flows between individuals but there were a number of significant differences between groups. The young control group had a mean (SD) unstimulated salivary flow of 0·53 (0·3 ml/min, which was significantly greater than any of the other groups ($p<0·001$ compared with the older group and the rheumatoid controls; $p<0·0001$ compared with patients with primary and secondary Sjögren's syn-



*Whole unstimulated flows (ml/min) in the five patient groups. Table 1 gives individual values. Each bar represents the mean (SD). Those marked * are significantly different from patients with primary Sjögren's syndrome (younger group, $p<0·0001$; older group, $p<0·02$; rheumatoid arthritis, $p<0·002$).*

drome. The old group had a mean (SD) flow of 0·3 (0·25) ml/min, which did not differ from the group with rheumatoid arthritis or from the patients with secondary Sjögren's syndrome. The flow for the older controls was significantly higher than for the group of patients with primary Sjögren's syndrome ($p<0·02$). Similarly the salivary flow of the rheumatoid patients did not differ from patients with secondary Sjögren's syndrome but was higher than the group with primary Sjögren's syndrome ($p<0·002$).

Although patients with primary Sjögren's syndrome had lower flows, they were not significantly different from the group with secondary Sjögren's syndrome. Patients with positive focal scores on a labial gland biopsy sample also had a lower mean (SD) flow (0·16 (0·2)) but it did not differ significantly from the flow in patients without positive results on a biopsy sample (0·23 (0·2)).

Using regression analyses there were no correlations between unstimulated flows and focus score, stimulated parotid flows, or duration of disease. There was, however, a significant correlation in the young control group between whole stimulated and whole unstimulated flows ($r^2=0·211$; $p<0·0001$). Also, when the data for all three control groups were pooled, there was a significant correlation between whole unstimulated salivary flow and age ($n=109$; $r^2=0·197$; $p<0·0001$).

The data for individual flows were further analysed by calculating the proportions of patients with a positive test when the criteria for positive was either 0·2 ml/min or less, or 0·1 ml/min or less. In the young control group only three subjects (4%) had whole unstimulated salivary flows less than 0·2 ml/min and one (1·4%) had a flow less than 0·1 ml/min. The values for the young control group were not used in the calculation of specificity and sensitivity because the data were not matched for age with the patients with Sjögren's syndrome.

In the age matched groups the older control group contained nine subjects (45%) with whole unstimulated salivary flows less than 0·2 ml/min and three (15%) with values less than 0·1 ml/min. The rheumatoid group had nine patients (45%) with a flow less than 0·2 ml/min but none less than 0·1 ml/min. Among the patients with Sjögren's syndrome 18 of 25 (72%) had a flow of 0·2 ml/min or less and 13 (52%) 0·1 ml/min or less. Six of eight (75%) of the group with primary Sjögren's syndrome and nine of 14 (64%) of the patients with a positive focus score had a flow of 0·1 ml/min or less. The sensitivity, specificity, and positive predictive values of the test for the two levels of positive results are given in table 3.

Table 3 Value of mean unstimulated salivary flow measurements in the diagnosis of Sjögren's syndrome

	Flow (ml/min)	
	≤0·1	*≤0·2*
Sensitivity (%)	52	68
Specificity (%)	92	55
Positive predictive value (%)	81	48

Values calculated from age matched controls only.

Discussion

The use of salivary flow for the evaluation of xerostomia has always been, and will probably remain, controversial. The main issues of concern are the relative merits of measuring stimulated or unstimulated flows or the measurement of whole saliva versus flow from individual glands. As there is so much variation in published reports and little agreement on what constitutes an abnormal flow, many clinicians consider it to be of no value. The method described in this study, however, is simple to perform, acceptable to patients, and needs no special equipment. In a similar way to Schirmer's test it can be performed easily in a busy clinic and the two tests together provide an immediate means of assessing the oral and ocular components of Sjögren's syndrome. Measurement of whole unstimulated salivary flows was successful in all subjects but attempts to measure the stimulated parotid flow were only successful in 13 of the 25 patients with Sjögren's syndrome. The main reasons for failure were detachment of the cannula or an inability of the patient to tolerate the cannula for the full 10 minute collection period.

A further concern is the specificity of the test and in this respect some workers dismiss its usefulness in Sjögren's syndrome because low flows are occasionally seen in normal subjects or may be due to other causes.[11] Sreebny *et al*[12] showed that 29% of patients attending a health centre had a dry mouth and that 54% of a sample of these had unstimulated whole flows of less than 0·1 ml/min. In a subsequent report, however, they showed that 69% of the sample were receiving drugs known to cause xerostomia and that this correlated with the low flows.[3] It is well established that drugs are the most common cause of dry mouth[6] but this cause can be excluded by taking a careful clinical history. Other important causes are psychiatric disturbances and irradiation damage, both of which can be excluded clinically. It must be realised that an abnormal flow is indicative of hyposecretion due to any cause and cannot be specific to any one disease.

In this study flows varied greatly between subjects but it was found that nearly 70% of patients with Sjögren's syndrome had a flow of 0·2 ml/min or less and 52% had a flow of 0·1 ml/min or less. This low flow was found in only 8% of controls making it a very specific test with a high predictive value of symptomatic xerostomia. Seventy five per cent of patients with primary Sjögren's syndrome had a flow of 0·1 ml/min or less and the mean flow in this group was less than the age matched normal controls or patients with rheumatoid arthritis. This suggests that a simple flow measurement may be useful in screening patients for possible primary Sjögren's syndrome if other causes of dry mouth have been excluded. Low flows were not found in the patients with rheumatoid arthritis. None had a flow of less than 0·1 ml/min and only nine of 20 had a flow of 0·2 ml/min or less. Thus the presence of a low flow may be particularly useful in establishing a diagnosis of secondary Sjögren's syndrome in rheumatoid patients.

It is controversial as to whether salivary flow decreases with age but the divergence of opinions appears to be due to the various sources of saliva and methods of collection. Previous studies have shown age has no effect on the flow of either stimulated or unstimulated parotid saliva,[14] or stimulated whole saliva.[15 16] The results of this study, however, confirm previous reports that whole unstimulated salivary flow decreases with age.[16–18] As the major contribution to the saliva content of the mouth and the comfort of the oral mucosa is from the constant unstimulated salivary flow, these findings almost certainly explain why a number of elderly subjects have a dry mouth and why whole unstimulated flows correlate with symptoms. The same subjects may have no difficulty eating because the stimulated parotid flow may remain normal.

This study has shown that a whole unstimulated flow of 0·1 ml/min or less is highly specific for symptomatic xerostomia associated with Sjögren's syndrome. As a diagnostic test for the oral component of Sjögren's syndrome salivary flow is useful if drugs are excluded as a cause and the results are interpreted in the context of the full clinical setting. For a patient with unequivocal rheumatoid arthritis and a dry mouth, the presence of a salivary flow of less than 0·1 ml/min is probably sufficient to establish a diagnosis of secondary Sjögren's syndrome. The diagnosis of primary Sjögren's syndrome is often more difficult and requires the unequivocal presence of the oral and ocular signs. In these instances salivary flow provides a useful and rapid screening test but a labial gland biopsy sample should also be taken to confirm the presence of lesions within the glands.

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