

Stimulated parotid salivary flow rates in normotensive, hypertensive, and hydrochlorothiazide-medicated African-Americans

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Stimulated parotid salivary flow rates were compared in elderly normotensive, hypertensive, and controlled hypertensive African-Americans, the latter group taking hydrochlorothiazide (HCTZ). The normotensive group consisted of 15 healthy unmedicated subjects with systolic blood pressures of less than 150 mm Hg and diastolic pressures less than 90 mm Hg. The hypertensive group consisted of 10 unmedicated subjects with systolic pressures greater than 160 mm Hg and diastolic pressures greater than 100 mm Hg. The controlled hypertensive group consisted of 20 subjects taking HCTZ (50 mg, daily) with controlled blood pressures similar to the normotensive control group. Stimulated parotid salivary samples were collected from each subject. A 2% citrate solution applied to the dorsum of the tongue was used for stimulation. The results showed no significant differences in stimulated parotid flow rates between normotensive and uncontrolled hypertensive subjects. However, the medicated, controlled hypertensive subjects had a significant reduction of stimulated parotid salivary flow rates compared to both the normotensive and hypertensive groups.

Key words: African-American; elderly; hypertension; parotid; saliva.

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The production of saliva by the major and minor salivary glands is essential for the maintenance and protection of the hard and soft tissues of the oral cavity and the inhibition of serious systemic pathogens (1, 2)

Although parotid salivary production seems to be unchanged by age (3), there are pharmaceuticals commonly used by the elderly which are thought to influence parotid salivary secretion (4,5). Specifically, antihypertensive, diuretic, and antidepressant medications commonly utilized by the elderly diminish salivary production (6-9).

The subjective complaint of mouth dryness xerostomia is commonly associated with the elderly, especially among individuals who have hypertension (10). Several investigators have attributed this symptom to the side effects result-

ing from the use of antihypertensive medication (2, 7). Hydrochlorothiazide (HCTZ), for example, has been shown to decrease stimulated whole saliva (11, 12). Further information regarding the effects of HCTZ on salivary function could not be found in the literature.

In addition to the paucity of information concerning HCTZ and salivary function, there is little information concerning salivary gland function in hypertensive individuals prior to use of antihypertensive medication. BEN-ARYEH *et al.* (13) reported higher unstimulated whole salivary flow rates in normotensive as compared to hypertensive patients prior to being treated with Pindolol. RAHN *et al.* (14) in a similar study, also found higher unstimulated whole salivary flow rates in normotensive individuals compared to mildly hy-

pertensive individuals prior to being placed on propranolol medication. Conversely, NIEDERMEIER *et al.* (15) found no differences in unstimulated and stimulated whole salivary flow rates in hypertensive subjects when compared to a normotensive control group. Therefore, there is no consensus on the influence of antihypertensive medication on salivary gland flow rates, and no information relevant to glandular secretions. Since whole saliva, in addition to glandular secretions, also contains food debris, desquamated epithelial cells, sputum, bacteria and their products, it is difficult to evaluate whole saliva and draw conclusions about glandular function (16).

Accordingly, the purpose of this study was to evaluate stimulated parotid flow rate, and parotid saliva for its

electrolyte constituents and the concentration of total IgA in normotensive, hypertensive, and HCTZ-treated individuals who were hypertensive prior to pharmacological therapy. The individuals in this study were all African-Americans, a segment of society known for its predisposition to hypertension (17, 18).

Material and methods

Population studied

The subjects participating in the study were from the Washington Village Medical Center. They were all African-Americans residing in the Southwest section of Baltimore City, Maryland. The participants were ambulatory patients seeking routine medical or dental care at the center, and were of low socio-economic class. Detailed demographic and social characteristics have been reported previously (19).

Subjects were divided into three groups depending on hypertensive status (Table 1). The individuals in the normotensive group (9 women, 6 men) were healthy and were not taking any prescription or non-prescription medication. The hypertensive group (2 women, 8 men) was otherwise healthy and not taking any medication. The HCTZ-medicated individuals (10 women, 10 men) were on HCTZ with a potassium sparing component, spironolactone, and no other medication.

HCTZ is a commonly prescribed antihypertensive used in the treatment of hypertension to reduce the expanded intravascular volume, which is a common cardiovascular clinical finding among African-Americans (17). All medicated individuals were on the same brand or type of medication. The HCTZ tablets were counted to ensure compliance with the therapeutic regimen.

Blood pressure determinations

Blood pressure measurements were taken on each person's right arm in a sitting position with a Baumanometer between 8 a.m. and 12 noon. Normotensive patients were categorized (20) as

having blood pressures of less than 150 mm Hg systolic and less than 90 mm Hg diastolic. Hypertensive individuals were those individuals who had systolic pressures greater than 160 mm Hg and diastolic pressures greater than 100 mm Hg. The hypertensive individuals in this study were found to have undiagnosed asymptomatic hypertension from routine hypertension screening. These individuals were immediately referred to the facility's attending physician for diagnosis and treatment. After being diagnosed with hypertension by the attending physician, the subjects were instructed to return to the center to receive their medication the next morning. In the uncontrolled hypertensive group stimulated parotid flow rates were collected prior to the initiation of medication.

The HCTZ group of individuals had been controlled with 50 mg daily of medication so that each person's systolic blood pressure was less than 150 mm Hg and the diastolic was less than 90 mm Hg. They had been on HCTZ therapy for at least two years.

Collection of saliva

Saliva was collected from the right parotid gland of all subjects between the hours of 8 a.m. to 12 noon using the Carlson-Crittenden Cup to control for circadian variation (22). Subjects from all three groups were equally distributed with respect to time of collection. The patients tested had not eaten, drank, or performed oral hygiene for at least two hours prior to collection of saliva. Stenson's duct was visualized and the cup positioned over the orifice. Stimulated saliva flow was observed for a two minute equilibrium period followed by a two minute period of actual salivary collection. A 2% citric acid solution was applied to the dorsum of the tongue every 30 seconds during the two minute equilibrium and the two minute collection periods. Samples were collected in pre-weighed plastic tubes and salivary output was determined gravimetrically (23). After the samples were weighed,

they were immediately frozen in liquid nitrogen.

Laboratory analysis

Sodium and potassium concentrations were measured by automated flame photometry while calcium and chloride levels were measured by automated spectrophotometry. Total protein values were obtained by spectrophotometry and total IgA concentrations by radial immunodiffusion. IgA secretion rates were determined by multiplying the salivary flow rate by the IgA concentration (24). All samples were analyzed at the same time to control for possible analytical variables (e.g. variance with assay kits, instruments, and analyst).

Statistical analysis

The data analysis used the SAS Statistical Software Package on a mainframe computer. Descriptive analyses were performed on the three groups (Tables 1 & 2). Analysis of variance was used to test for overall differences among groups for the mean levels of salivary flow rates and salivary constituents. Because of the unbalanced design of our study (i.e. unequal numbers of observations among the three groups), the PROC GLM (25) was used for the analyses. In the presence of significant overall group differences, paired comparisons were made to identify those particular groups that were significantly different from one another. The significance for these analyses was $p < 0.05$.

Results

Initial analyses found no differences in stimulated parotid flow rates between normotensive individuals and their hypertensive counterparts; however, both groups had a higher stimulated parotid flow rate than the HCTZ-medicated group, which was significant at the $p < 0.02$ and $p < 0.03$ levels respectively (Table 2). The normotensive and hypertensive groups also exhibited higher sodium levels, but only that for the hypertensive group was statistically significant, $p < 0.01$. The medicated group displayed a higher potassium level than the hypertensive group, $p < 0.005$. There were no differences in chloride, calcium, total protein, and total IgA concentrations among the three groups. However, the normotensive and hypertensive groups showed higher total IgA secretion rates than the HCTZ-medicated

Table 1. Mean values for blood pressures for normotensive, hypertensive, and HCTZ-medicated individuals

Group	n	Age	Systolic pressure mm Hg	Diastolic pressure mm Hg
Normotensive	15	69.5	146	76
Hypertensive	10	56.1	167	112
HCTZ medicated	20	68.5	138	87

Table 2. Comparison of SPFR and constituents for normotensive, hypertensive, and HCTZ-medicated individuals

Analysis	Normotensive (N) n = 15	Hypertensive (H) n = 10	Medicated (M) n = 20	F-value	t-value pair wise comparison	p value
Flow rate mL/min	0.695 ± 0.44 ¹	0.685 ± 0.39	0.422 ± 0.24	3.284	N > M = 2.38	p < 0.02
Sodium mmol/L	13.022 ± 14.59	20.53 ± 16.92	8.04 ± 6.58	p < 0.04 3.192	H > M = 2.27 H > M = 2.80	p < 0.03 p < 0.01
Chloride mmol/L	21.51 ± 7.07	20.79 ± 9.17	18.05 ± 6.58	p < 0.05 1.341		
Potassium mmol/L	21.53 ± 4.05	18.72 ± 3.48	22.82 ± 3.47	n.s. 4.132	M > H = 3.04	P < 0.005
Calcium mmol/L	4.65 ± 1.51	3.89 ± 0.91	4.85 ± 1.87	p < 0.02 1.229		
Tot. prot. mG/dL	52.0 ± 37.66	54.30 ± 26.03	67.47 ± 65.34	n.s. 0.308		
sIgA mG/dL	4.34 ± 3.87	3.06 ± 0.90	3.29 ± 0.44	n.s. 1.042		
sIgA rate µg/Min	27.56 ± 24.8	21.09 ± 11.70	12.69 ± 8.16	n.s. 3.337	N > M = 2.40 H > M = 3.34	P < 0.02 P < 0.05

¹ Standard deviation

² Not statistically significant

group. This was significant at the $p < 0.02$ and the $p < 0.05$ levels respectively.

Discussion

The results of this study demonstrate that the HCTZ-medicated African-Americans had significantly lower stimulated parotid flow rates compared to normotensive and hypertensive control groups, as well as a corresponding lower IgA secretion rate. It is important to consider these findings in view of the known mechanisms involved in salivary fluid secretion. Salivary fluid secretion involves two major steps: 1) an acinar stage yielding a primary saliva which is isotonic to that of plasma and 2) the transport of saliva through the duct system whereby constituent concentrations are altered, resulting in a final saliva which is hypotonic with respect to plasma (26). The primary saliva becomes hypotonic due to the extensive ductal reabsorption of Na^+ and Cl^- , and the modest secretion of K^+ and HCO_3^- (27). Primary fluid secretion depends on several distinct transport molecules, including the Ca^{++} activated Cl^- and/or HCO_3^- channel, the $\text{Na}^+/\text{K}^+/\text{Cl}^-$ cotransporter, the Ca^{++} activated K^+ channel, the Na^+/H^+ exchanger (where the enzyme carbonic anhydrase facilitates the intracellular conversion of CO_2 to HCO_3^-) and Na^+/K^+ ATPase (27, 28).

The specific nature of the chemical interaction between the thiazide diuretics and salivary transport molecules is not known; however, the benzothiadiazides are known to have carbonic anhy-

drase inhibiting diuretic properties (21). Indeed, HCTZ is a recognized carbonic anhydrase inhibitor with an IC_{50} of about 20 μM (21). HCTZ has a molecular weight of 223. At a dosage of 50 mg daily and an estimated cardiovascular volume of approximately 6 liters, a serum HCTZ concentration of approximately 29 μM is calculated, a value approximating its IC_{50} for carbonic anhydrase inhibition. This suggests a possibility that the fluid secretion inhibition observed here with the usage of HCTZ may be due to an inhibition of the HCO_3^- -mediated component of salivary fluid secretion (by blocking the formation of intracellular HCO_3^-). This would result in a reduction of salivary secretion, but not a complete inhibition because the Cl^- driven ($\text{Na}^+/\text{K}^+/\text{Cl}^-$ cotransport) component would still be functional and unaffected by HCTZ.

The lower salivary sodium concentration in the HCTZ medicated group could possibly be simply a secondary result of the decrease in the salivary flow rate. It is recognized that the $[\text{Na}^+]$ in saliva is flow rate dependent. As the salivary flow rate decreases, the sodium concentration also decreases due to increased sodium reabsorption in the ductal system (29). It is also possible that the reduced sodium level in the medicated group is the overall result of the renal effects of the HCTZ medication, which is designed to decrease sodium retention and thereby reduce systemic fluid retention (21).

Similarly, the elevated potassium level in the medicated group could be the result of the decreased stimulated parotid flow rate. A decreased stim-

ulated parotid flow rate would result in moderately higher salivary potassium levels due to increased rate of potassium secretion by the duct cells. Further research is obviously needed to determine the exact mechanism(s) by which the observed results occur.

The results of this study suggest that in individuals with hypertension taking HCTZ medication, a decreased stimulated parotid flow rate is secondary to the effect of the medication rather than the effect of the disease. The stimulated parotid gland flow rates in the HCTZ-medicated group were lower (40%) than in the normotensive and hypertensive groups, but were still within the normal ranges of saliva production as described by Ship *et al.* (30). Although it has been demonstrated that stimulated parotid flow rates undergo essentially no change over time in healthy persons (3), it is not known in what manner medication and disease may influence salivary physiology over time in an older adult (16). Consequently, it may be prudent for the oral health care practitioner to monitor the oral condition of HCTZ-medicated individuals of frequent intervals (31).

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