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ORIGINAL ARTICLE

Salivary constituents and acidogenic microbial counts in coronary artery bypass graft patients from baseline to three-years after operation

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Abstract Data on saliva in coronary artery bypass graft (CABG) surgery patients are sparse. Understanding salivary parameters, however, may aid clinical decision making. We hypothesized that cardiac surgery might affect patients' salivary flow rates and buffering, salivary proteins, and microbial counts. A 3-year, open follow-up study was conducted examining salivary flow, its chemical composition, and acidogenic microbial counts in 89 CABG surgery patients. The changes in salivary flow and proteins between baseline and 3-year post-CABG surgery were assessed using paired *t*-test and, with respect to the median of number of drugs used daily, by use of a nonparametric rank sum test. The results showed no long-term change in salivary flow rates and buffering capacity. With the exception of salivary urea, IgA and IgM concentration, and lysozyme output, the differences in salivary proteins between baseline and 3-year post-CABG were not statistically significant. No difference was observed in saliva values between patients taking drugs below or above the median number of drugs. Acidogenic microbial counts remained the same throughout the study. In conclusion, the salivary flow rates and constituents did not practically change in patients who underwent CABG surgery during the 3-year follow-up.

Keywords Saliva · Salivary proteins · Salivary microbial counts · Cardiovascular disease · Coronary artery bypass patients

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Introduction

Saliva with its moisturizing and lubricating action is the principal defense system in the mouth [6]. Reduced salivary flow not only affects general quality of life but also increases the risk of mucosal pathology such as inflammatory changes and candidiasis [31]. Patients with cardiovascular diseases (CVD) often take several xerogenic medicines daily including diuretics, beta-blocking agents, and angiotensin-converting enzyme (ACE) inhibitors, which, in turn, significantly reduce their salivary flow [7, 27]. Consequently, CVD patients may be at risk for increased oral diseases.

Although salivary flow and its other functions are important from the point of oral infection prevention, data on salivary secretion and composition in CVD patients

especially regarding postoperative salivary changes are sparse. It has been suggested that oral infections might even play a role in the development and progression of CVD, particularly atherosclerosis [13, 26]. Hence, properly functioning oral defense systems may be crucial for CVD patients irrespective of their disease phase or treatment mode.

Furthermore, saliva may be useful as a diagnostic tool [4, 7, 32, 37]. For example, albumin in saliva is an ultrafiltrate from serum, and analyzing its concentration can be useful in assessing oral mucosal integrity [12, 28]. We have observed that salivary albumin concentrations reflected the probability of the patient's survival in hospitalized elderly patients, and high concentrations of albumin may predict imminent mortality [25]. We have also previously reported results from cross-sectional analyses on saliva and occurrence of dental pathogens in a group of coronary heart disease (CHD) patients referred for coronary artery bypass graft (CABG) surgery and their matched, cardiologically healthy controls [23, 24]. The present paper describes the 3-year follow-up data of the CHD patients who underwent CABG surgery. We postulated that undergoing CABG operation might affect the patients' salivary flow rate and chemical and microbial composition because of the changing general health status. We have earlier shown that salivary lysozyme concentration may reflect risk of CVD [14]. Consequently, easily obtained saliva samples might be used to assess patient risk similarly to what has been suggested to be the case with C-reactive protein in blood [10, 29]. This would open new possibilities in clinical decision making in oral health care of patients with heart disease. However, basic reference data on saliva values are needed before further recommendations. This was the rational basis of the present investigation.

Materials and methods

Patients and the follow-up

Originally, 256 patients (60.3±9.3 years old, 64% men) meeting the following inclusion criteria were recruited: stable angina pectoris symptom, the severity of the heart disease of New York Heart Association (NYHA) grades II–IV [9], and no antibiotic drugs taken 30 days before the inclusion to this study. Patients with NYHA grade I disease and those who had received antibiotic treatment during the past month were excluded [23, 24].

The participants in the present study had been invited to take part in a 3-year follow-up study. The patients underwent elective CABG surgery at the Department of Cardiothoracic Surgery of the Kuopio University Hospital in Eastern Finland. Medical history and blood chemistry data were collected from the hospital records.

An experienced oral and maxillofacial surgeon (MQ) conducted both examinations, i.e., at baseline before admission to the cardiac care unit and at 3-year follow-up. At baseline, saliva samples were collected in the dental office of the hospital. The 3-year follow-up sampling took place at outpatient clinics close to the patients' area of residence. During the follow-up appointments, no detailed clinical or radiographic dental examinations could be carried out because dental equipment was not available. However, a visual dental examination and saliva sampling were conducted.

Ethical consideration

The study plan had been approved by the Joint Ethical Committee of the Kuopio University Hospital and the University of Kuopio. The guidelines of the Declaration of Helsinki were followed throughout. A written consent was obtained from all subjects.

Saliva collection methods

To avoid diurnal fluctuation, saliva was collected from the patients between 7 and 9 A.M. The patients had been advised not to eat or smoke 1 h before saliva sampling. For resting flow measurement, the free flow method was used. The patient was first asked to swallow initially and then let all the saliva flow into a 10-ml test tube during a 5-min period. Stimulated flow was collected by asking the patient to chew a standard 1-g piece of paraffin wax at an approximate rate of 60 per minute. Patients with prostheses kept them in the mouth during saliva sampling. Collection was started after 1 min of chewing and initial swallowing after which the final 5-min collection was started. Secretion rate was calculated as milliliters per minute. Only one examiner (MQ) supervised the saliva collection and measurement protocol according to our clinic practice [30].

Salivary analyses

Salivary buffering capacity was determined immediately after collection by using the Dentobuff-Strip® method (Orion Diagnostica, Espoo, Finland). End pH below 4.0 represents low buffering capacity in this method [2].

Salivary yeasts were assessed by using the Oricult-N® dip-slide method (Orion Diagnostica). The dip-slides were incubated at 20°C for 4 days, and yeast counts were assessed by using the semiquantitative scale provided by the manufacturer. Salivary *Streptococcus mutans* bacteria and lactobacilli counts were assessed by use of the Strip-Mutans® and Dentocult-LB®, respectively, according to

instructions of the manufacturer (Orion Diagnostica). The validity of these methods has been verified [2]. Salivary lysozyme was analyzed by using the agar diffusion method with *Micrococcus lysodeikticus* cells [30]. For this, fresh saliva was used. Remaining saliva samples were centrifuged for 15 min (1,800×*g* at 4°C); supernatants were deep-frozen and stored (−70°C) for later analyses.

Total salivary protein was measured by the colorimetric Lowry method. Albumin was analyzed by the colorimetric method of Webster [38] with human serum standards. Amylase was analyzed by using the Boehringer MPR 3 α-amylase EPS method (Boehringer Mannheim, Germany). Immunoglobulins (Ig) A, G, and M were analyzed with an enzyme immunoassay according to Lehtonen et al. [19]. Urea was analyzed with the Boehringer kinetic method (MPR2, Boehringer Mannheim). All analyses were performed immediately after thawing, and serum standards and controls were used in all the analyses.

Statistical methods

Using SAS version 8.2, the normality of salivary flow data were tested and observed that the underlying distribution was approximately Gaussian. Thus, to assess the changes in salivary flow and its composition, data were analyzed as one sample, correlated data of the two measurements using the paired *t*-test. Subgroup analyses were also conducted stratified by dentate status and gender. The null hypothesis was tested so that the mean population change was 0. Same variables, when relevant, were analyzed using nonparametric one-sample paired test. All other variables were tested in the same manner after transforming data into natural logarithms if needed to conform to normality. The effect on salivary parameters of the number of drugs used daily was analyzed by comparing values in patient groups below and above the median number of drugs. Nonparametric rank sum test was used. The *p* values below 0.05 were considered statistically significant in all analyses.

Results

Figure 1 shows the evolution of the present study from the baseline cohort. At baseline, 51% of the patients had hypertension, 11% reported current smoking, and 36% reported past smoking at baseline. Of these patients, 88.2% used beta-blocking agents, 83.7% used aspirin, 23.5% had calcium channel blocking agents, 82.3% used nitrates, and 6.7% received anticoagulants. Digitalis was in daily use by 8.4% of the patients, while 17.7% used diuretics daily. ACE blocking agents were used by 17.0%.

Between baseline and the 3-year post-CABG examinations, out of the original 256 patients, 33 (12.9%) persons died and 134 dropped out. The reasons for dropout were that (1) patients did not think dental follow-up was needed and (2) the patient felt too tired or (3) depressed to attend the follow-up examinations. Postoperative depression is known to be common in these patients [3]. At the 3-year follow-up examination of 89 remaining patients, 72 (81%) were men and 17 (19%) were women. Of the patients, 54 (61.4%) were dentate while 34 (38.6%) were edentulous at baseline. The mean number of teeth in the dentate was 13.1±8.1. There was no statistically significant change in the mean numbers of teeth during the follow-up.

Both stimulated and resting salivary flow in the whole group of patients decreased by calculation from baseline by −0.08 and −0.01 ml/min, respectively; but this decline was not statistically significant. The gender-specific means of salivary flows were as follows: in men, the resting flow rate was 0.23±0.11 ml/min at baseline and 0.21±0.15 ml/min 3 years later; in women, the respective values were 0.13±0.12 and 0.14±0.11 ml/min. Stimulated flow rates in men were 1.27±0.62 ml/min at baseline and 1.16±0.64 ml/min 3 years later. In women, the values were at baseline 1.03±0.66 ml/min and 1.08±0.69 ml/min 3 years later. Differences between men and women at baseline were statistically significant for resting salivary flow rate ($p<0.01$). No difference was observed in salivary buffering capacity between the baseline and 3-year follow-up samples as given in Table 1.

Table 2 shows the salivary protein concentration and output values at baseline and 3 years later. As shown, the protein output values and concentrations were slightly different. In most of the variables compared among the 89 patients who participated in both baseline and 3-year post-CABG examinations, we observed no statistically significant differences with the exception of salivary lysozyme, urea, and some immunoglobulin concentrations. When the data were analyzed stratified by dentate status and gender, the results did not change except that the difference in lysozyme concentration was no longer significant due to

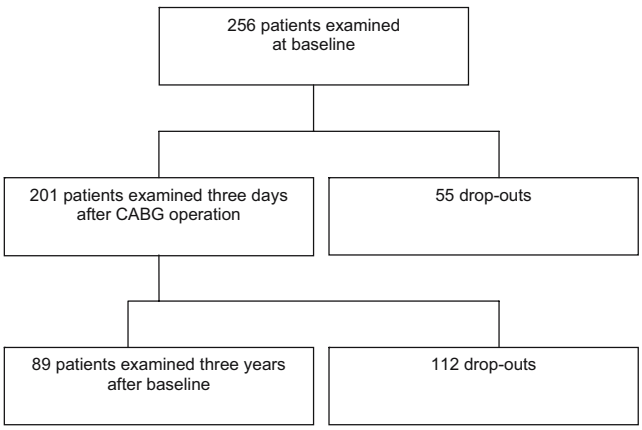

Fig. 1 Study profile of subjects investigated. *CABG*, coronary artery bypass graft

smaller sample size. The analyses of the effect of drugs on saliva values did not show statistically significant differences between the patients taking below or above the median number of drugs. The median number of drugs was three. However, patients with higher than median number of daily drugs had less decrease in salivary protein values as shown in Figs. 2 and 3. For example, decrease in salivary lysozyme was in the mean 16.3 units in the lower than median group in comparison to only 0.1 units in the higher than median group. Similarly, decrease in salivary albumin was 28.4 units in the lower and 12.4 in the higher than median group.

The findings on oral microorganisms analyzed are given in Table 3. No difference was observed in the number of patients with high lactobacilli and mutans streptococci counts during the follow-up. Although the number of patients with positive yeast counts decreased during follow-up, the difference was not statistically significant. More than half of the patients had positive yeast counts throughout the study.

Table 2 Salivary protein concentrations and outputs before and after coronary bypass operation (means with SD)

	Baseline	3 years after operation
Protein concentrations		
Total protein (mg/ml)	1.34±0.53	1.29±0.58
Lysozyme (μg/ml)	42.0±42.0	36.7±42.7
Amylase (U/ml)	110±78.2	106±79.4
Albumin (μg/ml)	169±131	178±164
Urea (mmol/l)	4.30±1.75	4.93±2.18*
IgA (μg/ml)	79.6±57.7	88.4±59.4**
IgG (μg/ml)	15.6±24.1	15.1±18.6
IgM (μg/ml)	3.37±3.31	4.61±6.82*
Protein outputs		
Total protein (mg/min)	1.60±1.05	1.39±0.80
Lysozyme (μg/min)	50.6±56.9	37.3±45.8**
Amylase (U/min)	139.4±142.2	119.6±101.4
Albumin (μg/min)	191.6±150.8	178.0±114.6
Urea (mmol/min)	299.3±1 90.6	304.0±172.0
IgA (μg/min)	80.2±42.1	85.1±48.2
IgG (μg/min)	16.2±23.2	13.6±12.6
IgM (μg/min)	3.27±2.80	4.19±5.30

*$p<0.01$
**$p<0.05$

Discussion

This was the first study investigating and following up salivary parameters in patients undergoing CABG operation. Hence, the present results give background for further studies in this group of patients. From the same hospital population as reported here, Jokinen et al. [16] observed an excellent 10-year survival rate in patients who underwent CABG operation. This demonstrated that CABG surgery has a good prognosis in the patients [17]. Nevertheless, the present findings were unexpected by not showing any clinically marked differences in the saliva parameters during the 3-year observation. We anticipated that an improvement in the patients' general health status due to cardiac surgery would reflect more clearly in saliva. In the clinical perspective, the observed statistically significant increase in urea, IgA, and IgM concentrations and the slight increase in salivary albumin were meaningless. The decrease in salivary lysozyme output, on the other hand, may reflect improvement in the cardiac health status. We have reported earlier that salivary lysozyme was associated with coronary artery disease [14]. In the stratified subgroup analyses of the present study, on the other hand, the small sample size inevitably decreased the statistical power of this investigation.

Table 1 Salivary flow and buffering capacity before and after coronary bypass operation (means with SD)

	Baseline	3 years after operation
Men ($n=72$)		
Salivary flow		
Unstimulated saliva flow (mean±SD)	0.22±0.12	0.20±0.15
Stimulated salivary flow (mean±SD)	1.27±0.61	1.16±0.64
Buffering capacity[a]		
Low	12 (17%)	14 (21%)
Medium	29 (40%)	21 (31%)
High	31 (43%)	33 (49%)
Women ($n=17$)		
Salivary flow		
Unstimulated saliva flow (mean±SD)	0.13±0.11	0.14±0.10
Stimulated salivary flow (mean±SD)	1.02±0.67	1.08±0.67
Buffering capacity[a]		
Low	3 (18%)	2 (13%)
Medium	6 (35%)	5 (33%)
High	8 (47%)	8 (53%)

[a] See "Materials and methods" for details.

Serum IgG specific to oral pathogens was associated with intima media thickness of carotid arteries [1]. However, salivary IgG is serum ultrafiltrate of the total antibody amount and our result cannot, therefore, be directly compared with these data. There are no studies on the association of salivary IgG and CVD. Sankar et al. [33] have studied 140 patients with Sjögren's syndrome but observed no meaningful associations between salivary factors and blood pressure.

Salivary albumin, in particular, has been linked with poor general prognosis of the patient. High salivary

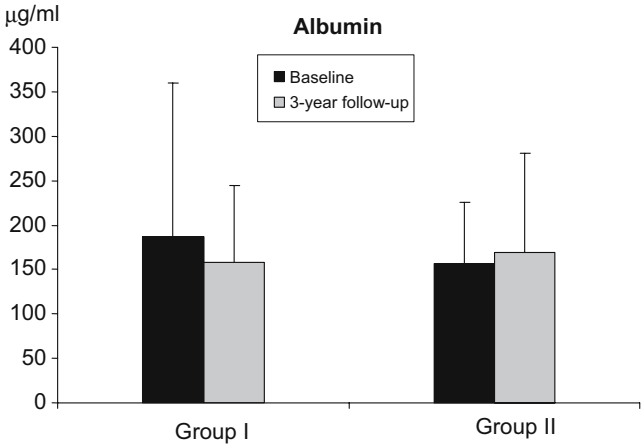

Fig. 2 Salivary albumin concentrations with standard deviations at baseline and 3 years later with respect to the number of drugs used daily in patients undergoing CABG surgery. Group I: mean number of drugs below the median. Group II: mean number of drugs above the median

albumin concentration might predict mortality of elderly patients and reflect systemic condition and degree of oral mucositis [5, 20, 22, 25, 34]. In the present study, however, albumin concentrations remained fairly stable between baseline and 3-year follow-up, and neither the patients' medication seemed to affect the albumin values. We would have expected a decline in salivary albumin reflecting the improvement in general health.

In the present study, we used routine biochemical methods of our laboratory in salivary analyses. Recently, methods have been presented for analyzing other salivary proteins such as salivary mucins [8] and proline-rich proteins, cystatins, histatins, and statherin [11]. It remains to be shown in future studies if these salivary components are affected by heart disease or its treatment as has been the case, for example, among irradiated patients.

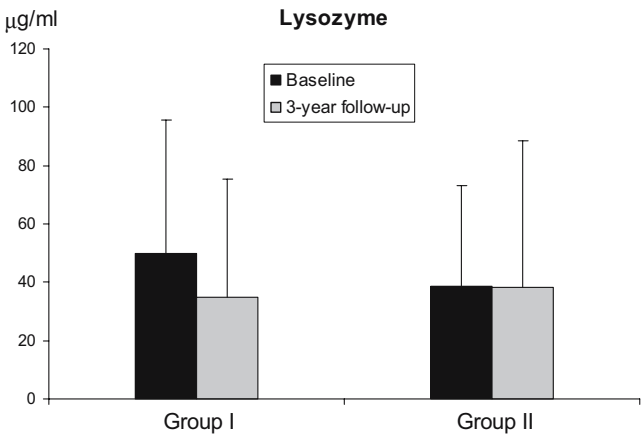

Fig. 3 Salivary lysozyme concentrations with standard deviations at baseline and 3 years later with respect to the number of drugs used daily in patients undergoing CABG surgery. Group I: mean number of drugs below the median. Group II: mean number of drugs above the median

In our clinic, reference values for hyposalivation are 0.1 ml/min for resting flow and 0.7 ml/min for stimulated flow, respectively [21]. The mean flow rates among the present study participants were clearly above these limits, even though the patients used many drugs daily. We did not analyze salivary flow rates with respect to individual drug preparations because of the relatively small material. It is known that the number of medicines taken daily is of principal importance among patients with reduced salivary flow [27]. Low salivary flow appears to also affect mucosal pathology as we have recently observed in a study among US veterans [15]. However, although some patients of the present study had significantly lower salivary flow rates than the clinical threshold in the present study, our results suggest that major surgical intervention need not affect salivary function. During convalescence, however, many of our patients had low salivary flow rates (data not shown).

The number of patients with reduced buffering capacity remained low throughout the study. This indicates a satisfactory general health status after CABG operation. The finding is also in agreement with earlier report of relative stability of salivary buffering capacity [35, 36]. The present microbiological results indicated that the open heart surgery did not cause any changes in the oral microecology during the 3 years of follow-up. Nevertheless, it should be emphasized that the majority of all patients harbored yeasts which, in the medically compromised state, may have systemic implications [18].

As regards the effect of the number of drugs used daily on salivary protein values, the trend was obvious, although not statistically significant, that decrease in protein concentrations was more pronounced in patients with less severe cardiac disease (the number of drugs was below the median). This may indicate an improvement both in general health status and in oral mucosal health. With a larger sample, the trend might have been more distinct.

The strength of the present study is the longitudinal design. The analyses used were based on standard and validated methods. An additional strength is that the same examiner performed both examinations and thus inter-examiner variability was avoided.

Table 3 Proportions of acidogenic microorganisms before and after coronary artery bypass graft operation

	Baseline (%)	3 years after operation (%)
High lactobacillus count (CFU > 10^5/ml)	39 (44)	38 (43)
High mutans streptococci count (CFU > 10^6/ml)	33 (38)	38 (43)
Positive yeast count	59 (66)	46 (52)

Weaknesses of the study are the open and observational design and the high dropout rate. The latter factor, on the other hand, was expected among the primarily hospitalized patients who, after their convalescent period, did not regard the dental checkup important anymore. Consequently, further patient education is needed to promote oral health as a part of overall health. We have earlier reported from the same patient cohort as reported here that their clinical oral health status was far from satisfactory when taken into the hospital [24]. Another weakness of our study is that the baseline and follow-up examinations were made in different locations and under different circumstances. Due to practical reasons, this was unavoidable, however. As no difference in salivary flow rates was observed between baseline and follow-up, the place of saliva collection probably did not affect the reliability of the measurements.

In conclusion, no clinically relevant differences were observed in salivary flow and in most salivary parameters analyzed in this 3-year study of the CABG-operated patients. Thus, the null hypothesis could not be rejected. However, the patients with high salivary yeast counts at baseline remained to have that high level throughout the study which aspect may need to be taken into account in clinical decision making. In general, CABG surgery did not cause long-term alterations in saliva. Our results give background data for future studies on patients with heart disease.

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