Utility of a Salivary Biosensor for Objective Assessment of Surgery-Related Stress

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Purpose: To evaluate the clinical utility of a salivary α-amylase (sAA) biosensor for assessing oral surgery-related stress responses and the differential effect of the personality trait of pain catastrophizing.

Patients and Methods: A prospective cohort study was conducted in 76 healthy subjects who underwent elective removal of their third molars. Along with subjects' self-reports of anxiety and pain, biosensor-facilitated measurements of sAA levels were obtained at multiple time points during the preoperative consult, surgery, and postsurgical follow-up visits. In addition, subjects completed the Pain Catastrophizing Scale at baseline. Mixed-effect regression models examined changes in sAA levels and self-report ratings within and across visits and the contribution of pain catastrophizing.

Results: The sAA levels were lower during surgery and postsurgical follow-up compared with the consult visit ($P < .01$). The sAA levels decreased during the surgery visit ($P < .05$) and did not change during the consult or follow-up visits. Individuals who reported greater helplessness to pain manifested higher sAA levels during the surgery visit ($P < .05$). Self-reported anxiety ratings were highest during the surgery visit, and pain ratings were highest during the follow-up visit.

Conclusions: The sAA levels did not show the predicted increases during the surgery visit compared with the consult and postsurgical follow-up visits or increases during the surgery visit. However, individuals who reported responding to pain with helplessness had higher sAA levels in anticipation of surgery, providing proof of concept for the value of point-of-care assessments of surgery-induced stresses and the differential effect of personality traits.

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Preoperative stress and anxiety are commonly experienced by individuals scheduled for removal of their impacted third molars, one of the most frequent surgical procedures performed in the United States.[1] Moderate levels of anxiety can help prepare patients for the distress of surgery; however, low levels of anxiety can leave the patient unprepared for postoperative pain and discomfort, whereas higher anxiety

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levels might sensitize the patient to noxious stimuli.[2,3] Importantly, individuals differ in their psychological and physiological responses to stress, in part because of underlying personality characteristics. In particular, pain catastrophizing, defined as the degree to which individuals magnify the pain experience and have difficulties coping effectively with pain, predicts increased pain ratings in the context of dental procedures.[4,5] Because a patient's orientation toward the painful stimuli and stressful experiences can significantly influence postoperative pain and discomfort, the ability to systematically recognize and assess psychological distress would allow the surgeon a more proactive and differentiated approach to pain management and improving the surgical experience.

The assessment of stress and anxiety is challenging because patients differ across personality characteristics, gender, culture, and prior surgical experience, which can modify the ways in which patients verbally express or report distress. As an alternative to subjective self-reports, stress researchers have increasingly focused on alternative methods that rely on quantifying the biological changes associated with the stress response.[6] One approach is measuring peripheral biomarkers of the neural response to stressful events. However, conventional methods for assessing the biological and physiological responses to stressful events rely on labor-intensive or expensive techniques, including psychophysiologic recordings and catecholamine assays from blood samples. Blood is the most commonly used biofluid of the biomarker assessments; however, the discomfort and pain associated with procuring a blood sample distorts the stress biomarker profile.[7] In contrast, saliva can be sampled noninvasively and easily and, as such, is an attractive alternative source of peripherally expressed stress biomarkers (eg, cortisol, α-amylase, and chromogranin-A).

Of the various putative stress markers manifesting in saliva, salivary α-amylase (sAA) has emerged as a potential surrogate marker of autonomic nervous system activity, with some data suggesting that sAA may be a specific marker of sympathetic nervous system activity generated by stress and anxiety.[8-10] Furthermore, increases in sAA levels can be elicited by sympathetic nervous system-activating drugs (yohimbine)[11] and decreased by β-blockade (propranolol).[12] Capitalizing on the biometric potential of sAA, the authors developed a portable sAA biosensor to allow a quick and easy point-of-care assessment of sAA levels.[13] The salivary biosensor, consisting of a miniaturized handheld analyzer and disposable saliva collector strips, does not need any elaborate preanalytical steps and provides rapid (<1 min) laboratory-quality measurements of sAA activity.[14] Such a device that permits an objective and a rapid point-of-care assessment of stress indicators could be valuable and relevant for the management of perioperative stress and the shaping of the surgical experience.

In a previous study, the utility of the sAA biosensor was explored for evaluating stress experiences in dental students by contrasting academic examination stress with everyday activities. The authors found that a higher biosensor-measured sAA level was related to higher ratings of concurrent self-reported distress.[15] The primary aim of the present study was to evaluate the clinical utility of the sAA biosensor for assessing the naturalistic stressful experiences surrounding third molar extractions. The authors hypothesized that biosensor-measured sAA levels would be increased during the surgical visit compared with the consult and follow-up visits. In addition, they hypothesized that individuals with greater pain catastrophizing would show higher sAA levels at all visits and during the surgery visit in particular. The authors also explored the relation between sAA levels and self-reported anxiety and distress.

Patients and Methods

PARTICIPANTS

Using a protocol approved by the institutional review board of the University of California, Los Angeles, the study enrolled 76 healthy participants 18 to 40 years old who presented to the oral and maxillofacial surgery clinic for the surgical extraction of at least 1 impacted third molar. Potential subjects were presented with the opportunity of joining in the study at the time of clinic registration and, if interested, they were screened and consented by a study personnel not affiliated with the participant's care. Eligibility criteria included the absence of any acute illnesses or chronic health conditions that could affect endocrine system function; never having been diagnosed with a psychiatric disorder; and nonuse of psychotropic medications, steroids, or illicit substances. All procedures were performed on an ambulatory basis, and patients were asked to refrain from eating and drinking for 8 hours before the procedure.

PROCEDURES

All study participants underwent 3 assessments conducted over 3 separate visits: preoperative consult, surgery, and postsurgical follow-up. During each visit, participants completed multiple psychological assessments and the sAA collection using the biosensor described below.

Preoperative Consult

All eligible and consented participants completed brief questionnaires before the actual consultation with the oral-maxillofacial surgeon, who was not involved in any data collection. Study personnel showed how the biosensor measurement was performed and provided instructions on how to self-report subjective ratings of anxiety, pain, and calmness. Four sAA readings and subjective ratings were obtained: *1)* immediately after the participants received a summary of the procedures; *2)* when the participant arrived in the consult room; *3)* after the surgeon completed the clinical examination and made the treatment recommendation; and *4)* following 5 minutes of resting after the surgical consultation was complete.

Surgery

During the surgical visit, 4 sAA readings and subjective ratings were obtained: *1)* shortly after participants arrived at the clinic; *2)* after research personnel reviewed the study procedures; *3)* after arrival in the surgical suite for the surgical procedure; and *4)* before local or general anesthetic was applied. No samples or measurements were obtained from the participants during or after the application of the anesthetic or during or after the surgical procedure. Surgical techniques varied depending on the surgeon and the complexity of impaction. Postoperative medications included a narcotic analgesic and an antibiotic.

Postsurgical Follow-Up

At a follow-up visit conducted 1 week after surgery, study personnel repeated the sAA readings and subjective ratings at time points similar to the preoperative consult visit. Data were not collected on postoperative complications such as dry socket.

MEASUREMENTS

Pain Catastrophizing

All participants completed the Pain Catastrophizing Scale (PCS)[16] during the initial preoperative consult. The 13-item PCS measures the degree to which individuals cope with painful experiences, with cognitive activities that exacerbate the fearful aspects of their pain experience: rumination (excessive focus on the pain sensation), magnification (exaggeration of threat), and helplessness (feeling helpless to control the pain symptoms). Respondents report the degree to which they experience various thoughts and feelings during painful experiences on a 5-point Likert scale, with scoring possibilities ranging from "not at all" (0) to "always" (4). The total score ranges from 0 to 52, and high scores indicate that more catastrophic thoughts or feelings are experienced. The PCS has been used successfully in a variety of experimental and clinical settings and is one of the most widely used measurements of this construct. It has excellent psychometric properties and is considered a reliable and valid measurement (eg, $\alpha = 0.87$).[16]

Salivary α-Amylase

The direct measurement of sAA was accomplished with a colorimetric salivary biosensor developed and validated previously.[13,14] The sAA biosensor consists of disposable saliva collector strips and a handheld reader with integrated analytic and reporting capabilities. The saliva collector strip is placed under the tongue, allowed to saturate with saliva for 15 seconds, and then removed and inserted into the handheld reader. Algorithms, inputted into the biosensor's central processing unit, normalize variations in ambient temperature and salivary pH, and the measured sAA levels are shown on the digital display of the reader.[14] To minimize variations, participants were instructed not to chew or otherwise manipulate their tongue or mouth shortly before and during the saliva sampling.

Subjective Self-Reports

During each visit, participants completed multiple single-item self-reports of anxiety, pain, and calm during each saliva sample. Participants rated each item ("How anxious do you feel right now?" "How much pain do you feel right now?" and "How calm do you feel right now?") on a scale from 1 (not at all) to 8 (extreme).

STATISTICAL ANALYSES

Unless otherwise specified, statistical tests involving sAA levels used $\log_e$ transformed data, where e was the sAA level obtained from the biosensor. Data analyses were performed using SAS 9.2 (SAS Institute, Cary, NC). Using mixed-effects models with a random intercept and a first-order autoregressive covariance structure for repeated measures, the sAA levels were examined for any changes within and among the 3 visits. The changes in self-reported pain, anxiety, and calmness ratings, collected 4 times within each visit, were also investigated using mixed-effects models with the same structure. The t statistics reported are for the fixed-effects parameters within these mixed-effects models. Mixed models were built using the $\log_e$ transformed sAA readings as the outcome, with PCS, self-reported anxiety, pain, and calmness, and time as covariates. Other mixed models examined the relation between PCS subscales and changes in self-reported anxiety, pain, and calm over time.

Results

PARTICIPANT CHARACTERISTICS

Most of the 76 subjects enrolled were young (mean, 24.6 yrs old; standard deviation [SD], 5.2 yrs), and there were more women participants (64.5%) than men (35.5%). Most subjects (64.8%) had at least 3 third mo-

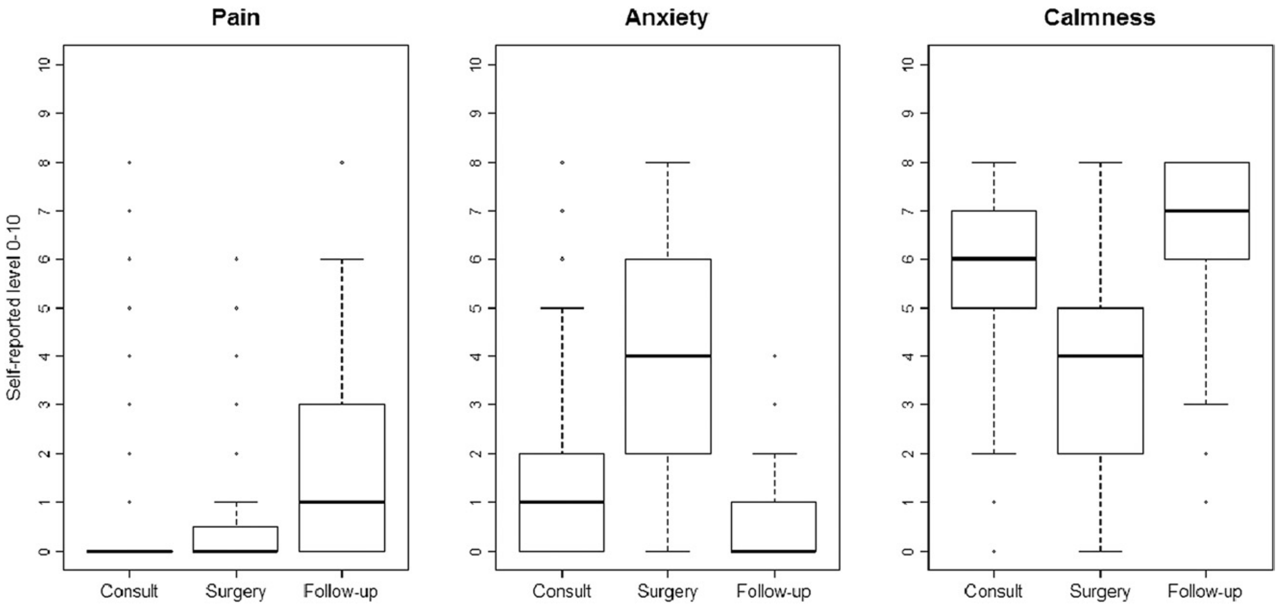

FIGURE 1. Boxplots illustrating self-reported pain, anxiety, and calmness levels during each visit. Self-report ratings were averaged within each visit.

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lars removed surgically at the same appointment. The total pain catastrophizing scale scores obtained at the baseline visit ranged from 0 to 32 (mean score, 14.39; SD, 9.8), with scores on the 3 subscales of the PCS as follows: rumination—mean, 6.1; SD, 4.4; range, 0 to 16; magnification—mean, 3.1; SD, 2.2; range, 0 to 8; helplessness—mean, 5.2; SD, 4.6; range, 0 to 21.

SUBJECTIVE RATINGS OF STRESS AND PAIN

Figure 1 presents the changes in the participants' self-ratings for pain, anxiety, and calmness across the 3 visits. Focusing on changes across visits, the pain ratings did not differ between the preoperative consult and surgery visits (the pain assessments were completed before the surgical procedure) but were significantly higher during the follow-up visit (t = 5.78, $P < .0001$). Compared with the consult visit, the anxiety ratings were higher during the surgery visit (t = 10.73, $P < .0001$) and lower during the follow-up visit ($t = -3.47$, $P = .0005$), whereas the calmness ratings were significantly lower during the surgery visit ($t = -8.17$, $P = .0001$) and higher during the follow-up visit ($t = 3.32$, $P = .0009$).

The relations between the PCS scores and the subjective ratings during the various visits were examined (Table 1). The PCS total score and 3 subscale scores were not significantly related to pain during the visits. The PCS total score and the rumination and helpless subscales were related to higher anxiety ratings during the consult and surgery visits and to lower calmness ratings during the consult visit. Higher magnification scores were also related to lower calmness

Table 1. RELATIONS BETWEEN PCS SUBSCALES AND SUBJECTIVE RATINGS AT EACH VISIT

	Consult			Surgery			Follow-Up		
PCS Subscale	Pain	Anxiety	Calm	Pain	Anxiety	Calm	Pain	Anxiety	Calm
Total score	−0.02	0.047†	−0.062‡	−0.01	0.09‡	−0.05*	−0.02	0.02	−0.01
Helplessness	−0.03	0.095†	−0.12‡	−0.03	0.19†	−0.13†	−0.06	0.04	−0.04
Magnification	−0.07	0.13	−0.22†	0.04	0.23	−0.14	−0.07	0.05	−0.09
Rumination	−0.05	0.097†	−0.12†	−0.03	0.19†	−0.1	−0.02	0.04	−0.02

Note: Parameters are unstandardized coefficients showing the relation between the PCS subscale of interest and the subjective rating of interest at each visit. Coefficients represent the change in subjective ratings associated with a 1-U change in the PCS subscale of interest. Analyses were conducted separately for each PCS subscale.

Abbreviation: PCS, Pain Catastrophizing Scale.

*$P < .05$, †$P < .01$, ‡$P < .001$.

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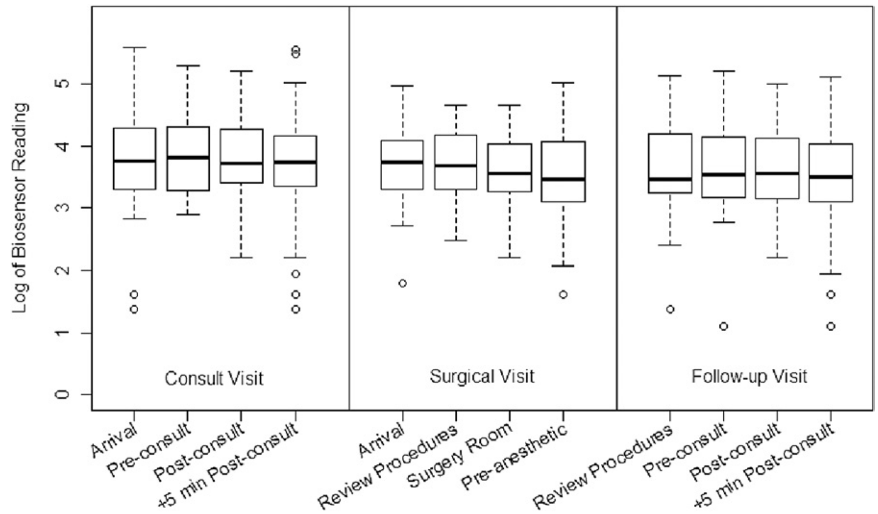

FIGURE 2. Boxplots depicting salivary α-amylase levels during each visit.

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ratings during the consult visit. In the surgery visit, the PCS total score and helplessness subscale were associated with lower calmness ratings.

TEMPORAL CHANGES IN sAA LEVELS

Boxplots showing average sAA levels at each visit are shown in Figure 2. The mixed models showed that the mean sAA levels during the surgery visit were an average of -0.12 log(1 + U/mL) lower compared with the consult visit ($t = -2.58$, $P = .01$) and mean sAA levels during the follow-up visit were an average of -0.16 log(1 + U/mL) units lower compared with the consult visit ($t = -3.28$, $P < .001$). Changes in sAA levels within each visit also were examined. The levels of sAA did not significantly change during the consult or follow-up visit. During the surgical visit, the sAA levels did not change significantly from arrival at the clinic to the informed consent process but showed a significant decrease once participants arrived in the surgical suite and just before the application of the anesthetic ($\gamma = -0.095$; standard error, 0.04; $t = -2.23$; $P = .03$).

RELATIONS BETWEEN PCS AND sAA LEVELS

Whether the different facets of pain catastrophizing predicted the sAA measurements was examined within each visit. The magnification and rumination subscales did not predict sAA levels (data not shown), and the total score showed a trend for greater catastrophizing related to higher sAA levels during the surgery visit ($\gamma = 0.008$, $t = 1.77$, $P = .08$). The helplessness subscale emerged as a signif-

Table 2. PARAMETER ESTIMATES FROM MIXED REGRESSION MODELS PREDICTING sAA LEVELS FROM VISIT AND PCS HELPLESSNESS SUBSCALE SCORES

Parameter	Estimate	SE	*t* Statistic	*P* Value
Fixed parameters				
Consult (average sAA level)	3.78	0.10	38.06	<.0001
PCS helplessness × consult	0.004	0.01	0.23	.79
Surgery (difference from consult)	−0.23	0.07	−3.39	.0007
PCS helplessness × surgery	0.02	0.01	2.22	.03
Follow-Up (difference from consult)	−0.17	0.07	−2.31	.02
PCS helplessness × follow-up	0.002	0.01	0.22	.82
Variance parameters				
Intercept variance	0.25			
AR(1) variance	0.23			
Residual variance	0.21			

Note: Parameters are unstandardized coefficients. The PCS helplessness × visit (consult, surgery, follow-up) interactions indicate the relation between the PCS helplessness scores and the sAA levels averaged across the visit.

Abbreviations: AR(1), first-order autoregressive; PCS, Pain Catastrophizing Scale; sAA, salivary α-amylase; SE, standard error.

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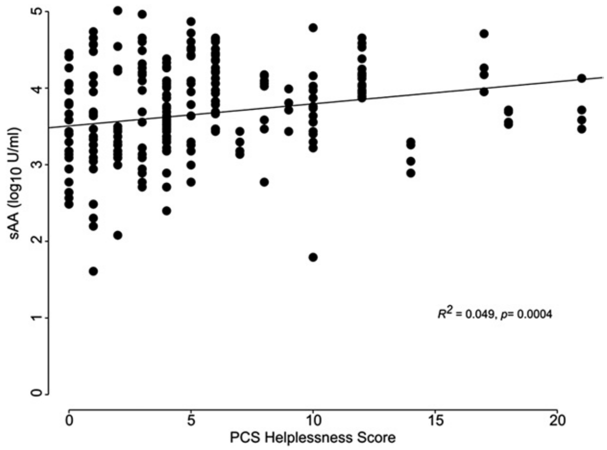

FIGURE 3. Scatterplot indicating the relation between scores on the Pain Catastrophizing Scale (PCS) helplessness subscale and salivary α-amylase (sAA) levels during the surgery visit.

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icant predictor of sAA. As presented in Table 2, greater helplessness ratings predicted higher sAA levels during the surgery visit. Figure 3 shows that a 1-point increase in helplessness ratings was related to a 0.026 log(U/mL) unit greater average sAA during the surgery visit.

RELATIONS BETWEEN SUBJECTIVE RATINGS AND sAA LEVELS

Based on previous work suggesting that greater subjective distress is concurrently related to higher sAA levels,[8,17] the relation between self-reports of anxiety, calm, and pain ratings and sAA levels was explored. Anxiety and calmness ratings were not related to sAA levels. Greater pain ratings were related to lower sAA levels ($\gamma = -0.04$, $t = -2.53$, $P = .01$). When the relations between pain ratings and sAA levels within each visit were examined, higher pain ratings during the consult visit were related to lower sAA levels ($\gamma = -0.08$, $t = -3.36$, $P = .0008$). Pain ratings during the surgery visit were not related to sAA levels, and higher pain ratings during the follow-up visit were related to higher sAA levels ($\gamma = 0.099$, $t = 3.33$, $P = .0009$).

Discussion

Recently developed portable biosensors that allow the rapid point-of-use measurement of putative stress biomarkers have the potential to help clinicians objectively ascertain stress and anxiety levels preoperatively and anticipate pain-control issues. To expand their studies of the clinical utility of such stress biosensors in naturalistic settings,[14,15] the authors evaluated the prototype sAA biosensor in the context of the surgical extraction of impacted third molars. Contrary to the authors' initial premise, sAA levels did not show the predicted increase during the surgery visit compared with the consult or follow-up. Subjective ratings of anxiety, pain, and calmness changed in expected directions at each visit; however, sAA levels were actually lower during the surgery visit compared with the initial consult visit and similar to levels during the follow-up visit. Notably, sAA levels did not show significant changes during the course of the consult or follow-up visit and decreased during the surgery visit before the administration of the anesthetic. In contrast to the authors' previous investigations of sAA levels in dental students,[15] where they found that sAA levels were related to concurrent self-reported anxiety in the context of academic stress, sAA levels in the context of a surgical procedure were not related to self-reported anxiety. At the same time, higher pain ratings at the follow-up visit were related to higher sAA levels.

One distinctive finding was pain catastrophizing and sAA levels. In particular, individuals who reported that they react with helplessness during pain experiences, such as feeling like pain was unending, overwhelming, and uncontrollable, had higher sAA levels in anticipation of the third molar surgery. The most plausible mechanism connecting pain catastrophizing with sAA responses involves the neural regions that regulate pain-related information processing. Several regions of the brain are critically involved in a circuit that processes the affective, attention, and sensorimotor aspects of pain, including the anterior cingulate and insula. Indeed, during mild acute pain, greater activity in those regions has been related to higher self-reported pain catastrophizing scores.[18] Many of the same regions have been implicated in autonomic nervous system regulation, with the strongest evidence for cardiovascular measurements of autonomic activity.[19,20] Thus, increased activity in the circuit related to magnifying the pain experience may also lead to stimulation of the central autonomic network, leading to increased sympathetic activity. To the authors' knowledge, this is the first presentation showing that catastrophizing influences physiologic responses in the context of a naturalistic pain-salient setting. Taken together with the results from the authors' primary analyses, the present data suggest that sAA responses to a naturalistic stressor may not occur normatively for most individuals. Instead, for certain types of stressors, sAA responses and other sympathetic nervous system responses to surgery may occur only in individuals with particular vulnerabilities, such as pain catastrophizing.

The authors also found that the mean sAA levels were lower during the surgical visit compared with the consult and follow-up visits, due in part to a decrease in sAA over the course of the surgery visit. One possible explanation for these observed findings is that for many participants, the adrenergic response to the pending surgery may have peaked during or even before participants arrived at the clinic. Simply stated, perhaps the anticipation of the surgery visit and even the effort expended in arriving to the clinic (eg, rushing to be on time) could have led to an increase in autonomic activity, which then decreased over time as the patients arrived at the clinic and were able to acclimate to the setting. Unfortunately, few studies have directly addressed the dynamics of the autonomic responses to naturalistic events, that is, changes in autonomic responses before, during, and after a stressor in the naturalistic environment. Indeed, obtaining an adequate baseline is one of the challenges to studying physiologic responses to naturalistic stressors. In contrast, in experimental stressor studies conducted under controlled laboratory conditions, participants are frequently allowed to acclimate to the environment for periods of 20 to 30 minutes so that neuroendocrine and autonomic activity related to arriving to the laboratory can return to baseline. For future work with similar types of stressors (ie, clinic appointments), the authors suggest obtaining samples from participants before arrival to the clinic.

In addition to a significant decrease in sAA levels during the surgery visit, sAA levels did not show significant changes during the consult or follow-up visit. As described earlier, one possible explanation is that sAA levels at arrival to the clinic were not true baseline levels but were actually higher than the individual's resting baseline and remained higher throughout the visit. However, the more likely explanation is that the consult and follow-up visits did not elicit a significant increase in autonomic activity. Indeed, the literature suggests that sympathetic activation during stress is conditioned on the level of mental effort exerted during the stressor. Given that in the consult and follow-up visits very little mental or physical effort is expended by the patients and that other traditional dimensions of a stressor (eg, controllability, novelty, social-evaluative threat) are at relatively low levels, it may not be surprising to see no change in sAA levels during the nonsurgical visits. An alternative explanation may be that the sAA level is not an exclusive readout of sympathetic activity. Whole-mouth sAA can be viewed as the sum of many contributing factors, including sympathetic-adrenergic stimulation during stress and parasympathetic activity. In general, sympathetic activation of the parotid gland produces a degranulation of the preformed amylase stored as secretory granules in the acinar cells, and the product is secreted by exocytosis into the saliva to increase the salivary amylase concentration. However, a considerable amount of sAA can also be produced through parasympathetic activation through a process that does not involve acinar cell degranulation.[21,22]

Although the present approach to examining a stressor in the naturalistic environment provides an ecological valid examination of sAA responses to stress, the approach has some limitations. As described earlier, the authors did not have an adequate measurement of baseline sAA activity before the patients' arrival at the clinic, such as a measurement of sAA at the same time on a different day. Moreover, sympathetic activity may have peaked during the surgery, but because the nature of the surgery precluded obtaining saliva samples, the authors did not have a measurement of postsurgical sympathetic activity. Although there were restrictions on eating and drinking before the surgery, there were no similar restrictions before the consult or follow-up visit. Thus, the fact that the present results were limited to the surgery may have been from confounding factors that influenced sAA levels during the consult and follow-up visits.

CLINICAL IMPLICATIONS

Point-of-care biosensor systems such as the sAA biosensor may potentially improve patient care by allowing surgeons to measure and analyze patterns of stress-related biomarkers. In combination with measurements of underlying differences in cognitive and emotional processing of the surgical experience, such as pain catastrophizing, care providers will be able to anticipate pain-control issues, thus allowing individualized antianxiety strategies and pain medications. Thus, portable stress measurement devices such as the sAA biosensor that use biological indicators to monitor underlying psychological differences and predict a patient's postoperative response may eventually result in better pain control in surgical patients and thus improve patient care and satisfaction.

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