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ORIGINAL ARTICLE

The use of electrodermal activity in pulpal diagnosis and dental pain assessment

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Abstract

Aims: To explore whether electrodermal activity (EDA) can serve as a complementary tool for pulpal diagnosis (Aim 1) and an objective metric to assess dental pain before and after local anaesthesia (Aim 2).

Methodology: A total of 53 subjects (189 teeth) and 14 subjects (14 teeth) were recruited for Aim 1 and Aim 2, respectively. We recorded EDA using commercially available devices, PowerLab and Galvanic Skin Response (GSR) Amplifier, in conjunction with cold and electric pulp testing (EPT). Participants rated their level of sensation on a 0–10 visual analogue scale (VAS) after each test. We recorded EPT-stimulated EDA activity before and after the administration of local anaesthesia for participants who required root canal treatment (RCT) due to painful pulpitis. The raw data were converted to the time-varying index of sympathetic activity (TVSymp), a sensitive and specific parameter of EDA. Statistical analysis was performed using Python 3.6 and its Scikit-*post hoc* library.

Results: Electrodermal activity was upregulated by the stimuli of cold and EPT testing in the normal pulp. TVSymp signals were significantly increased in vital pulp compared to necrotic pulp by both cold test and EPT. Teeth that exhibited intensive sensitivity to cold with or without lingering pain had increased peak numbers of TVSymp than teeth with mild sensation to cold. Pre- and post-anaesthesia EDA activity and VAS scores were recorded in patients with painful pulpitis. Post-anaesthesia EDA signals were significantly lower compared to pre-anaesthesia levels. Approximately 71% of patients (10 of 14 patients) experienced no pain during treatment and reported VAS score of 0 or 1. The majority of patients (10 of 14) showed a reduction of TVSymp after the administration of anaesthesia. Two of three patients who experienced increased pain during RCT (post-treatment VAS > pre-treatment VAS) exhibited increased post-anaesthesia TVSymp.

Conclusions: Our data show promising results for using EDA in pulpal diagnosis and for assessing dental pain. Whilst our testing was limited to subjects who had adequate communication skills, our future goal is to be able to use this technology to aid in the endodontic diagnosis of patients who have limited communication ability.

Hanh T. Tran and Youngsun Kong contributed equally to this study and should both be listed as the first authors.

KEYWORDS
electrodermal activity, endodontics, pain assessment, pulpal diagnosis

INTRODUCTION

Dental caries is the most prevalent oral disease, affecting almost half of the world's population (Vos et al., 2017). Bacteria from caries egress into root canals leading to infection of the pulp and the periapex (tissue surrounding root tips), causing hypersensitivity, severe pain and can lead to systemic upset and morbidity. To date, no objective and quantitative measure for dental pain exists. Patients express their pain most commonly by a subjective metric, visual analogue scale (VAS). The VAS is a 0–10 scale, with 0 denoting no pain and 10 denoting the worst pain imaginable. One of the obstacles to studying the efficacy of pain medication is a lack of means to quantitatively measure pain. Moreover, the selection of analgesics for toothache is partially patient driven, which may lead to opioid abuse. There is a critical need to develop an objective metric with high sensitivity and specificity for dental pain.

Patients who suffer from odontogenic infection with or without pain should be treated early before further devastating symptoms and bone loss develops. Accurate diagnosis of affected teeth is essential for appropriate treatment but can be challenging because (1) dental pain can spread to neighbouring teeth or tissues (Falace et al., 1996; Konzelman et al., 2001; Yoon et al., 2001); (2) nondental pain, such as sinusitis, can mimic toothache (Farella et al., 2002; Law & Lilly, 1995; Murayama et al., 2009); and (3) pulpal tests rely exclusively on patient responses. Current pulp vitality tests include cold and electric pulp test (EPT). Cold testing causes an outward flow of dentinal tubular fluid and stimulates Aδ nerve fibres (Trowbridge et al., 1980). EPT functions by conducting a current through the tooth to stimulate Aδ nerve fibres. Both cold and EPT tests are not 100% accurate in determining the pulpal status. Diseased teeth can be identified 87% and 72% of the time by cold test and EPT respectively (Mainkar & Kim, 2018). In addition, 84% of healthy pulp tissue has a positive sensation to cold without lingering pain and 93% of vital pulp responds to EPT (Mainkar & Kim, 2018). Despite relatively high sensitivity and specificity, vitality tests are often inconsistent or inconclusive in patients who are unable to communicate, such as young children and patients with mental disabilities or a language barrier. An automated recording of patients' responses to pulp vitality tests remains an unmet need in endodontic diagnosis.

In this study, we aim to examine whether electrodermal activity (EDA) can be a physiomarker for dental pain by testing its use in pulpal diagnosis and endodontic pain assessment before and after the administration of local anaesthesia. EDA, known as galvanic skin response (GSR), is a measure of changes in the electrical conductance of the skin, highly associated with sweat gland activity modulated by the sympathetic nervous system (SNS) (Krogstad et al., 2006; Tronstad et al., 2008). There are two types of sweat glands. Apocrine sweat glands are distributed in the axillae, fossa, areola, eyelids and perianal regions. Eccrine are on all skin and located nearer to the dermal surface than apocrine sweat glands (Baker, 2019). Based on physiological characteristics and convenience, we measured EDA by attaching two electrodes on the index and middle fingers, known as exosomatic approach (Gersak & Drnovsek, 2020). EDA exclusively measures activities of SNS within sub-seconds of SNS-altering events (Chon et al., 2014; Posada-Quintero et al., 2017, 2019; Posada-Quintero, Bolkhovsky, et al., 2018; Posada-Quintero, Florian, et al., 2018; Posada-Quintero, Florian, Orjuela-Canon, Aljama-Corrales, et al., 2016; Posada-Quintero, Florian, Orjuela-Canon, & Chon, 2016; Posada-Quintero, Reljin, et al., 2018). Stress and noxious stimuli (e.g. thermal, electrical and forearm ischemia) enhance sudomotor innervation causing EDA to increase (Leonard et al., 2015; Maixner et al., 1990; Piovesan et al., 2018). Because EDA exclusively reflects SNS activity, it is more sensitive to nociceptive pain than heart rate and blood pressure, which are affected by both the SNS and PNS (Storm, 2008). We hypothesize that EDA activity can serve as a sensitive and specific measure for dental pain based on: (1) sympathetic post-ganglionic innervation of pulpal blood vessels found adjacent to odontoblasts, predentin and the deeper parts of pulp (Aars et al., 1993; Inoue et al., 1992; Johnsen & Johns, 1978; Nair, 1995); (2) increased pulpal blood flow upon electrical stimulation modulated by the SNS (Hargreaves et al., 2003); (3) sympathetic nerve fibre sprouting in inflamed pulp (Haug & Heyeraas, 2003) and (4) the dental pulp having little or no parasympathetic nervous system (PNS) function (Sasano et al., 1995). EDA has been used to assess various types of pain, such as orthopaedic, arthritic, visceral and postoperative pain but not dental pain (Bradley et al., 2008; Choo et al., 2010; Eriksson et al., 2008; Gruss et al., 2015; Loggia et al., 2011; Rialland et al., 2012; Richardson et al., 2007; Schestatsky et al., 2007; Storm, 2008; Susam et al., 2018; Turner et al., 2013). EDA has been used in the assessment of dental anxiety but not dental pain (Chen et al., 2014; Pop-Jordanova et al., 2018; Shapiro, Melmed, et al., 2009; Shapiro, Sgan-Cohen, et al., 2009).

Electrodermal activity measurement can be divided into tonic and phasic responses. Tonic responses represent

baseline EDA levels, whilst phasic responses are rapid changes resulting from SNS stimulation. Multiple indices can be used for the evaluation of EDA, including the skin conductance level (SCL), the nonspecific skin conductance responses (NS.SCRs), the time-varying index of sympathetic activity (TVSymp), the modified time-varying index of EDA (MTVSymp) and others. TVSymp quantifies the phasic response of EDA, and is calculated using a high-pass filter (0.01 Hz), variable frequency complex demodulation and the Hilbert transform. TVSymp is a reconstructed EDA signal with EDA frequency bandwidth associated with sympathetic tone (0.04–0.25 Hz), and is one of the most sensitive indices with high consistency compared to other EDA indices (Posada-Quintero, Florian, Orjuela-Canon, Aljama-Corrales, et al., 2016; Posada-Quintero, Florian, Orjuela-Canon, & Chon, 2016). We converted EDA raw data to TVSymp signals to analyse its usefulness in dental applications.

We examined whether TVSymp can serve as a complementary diagnostic tool to identify teeth requiring root canal treatment (RCT) due to distinctly different patterns from a normal and infected pulp. We further assessed whether TVSymp would be a reliable indicator of anaesthetic success in teeth with a diagnosis of symptomatic irreversible pulpitis. Traditional signs of anaesthetic success include subjective signs of lip and tongue numbness, a lack of sensation to being pricked with a sharp instrument around the mucosa of the affected tooth and no sensation to pulp vitality tests. However, these methods have been shown to be unreliable in predicting pulpal anaesthesia (Certosimo & Archer, 1996; Dreven et al., 1987; Hinkley et al., 1991; McLean et al., 1993). Our data suggested that TVSymp has the potential to reflect pulpal responses to cold and EPT testing as well as to confirm the reduction in pain after successful local anaesthesia.

MATERIALS AND METHODS

Patient enrolment

All human studies were in accordance with the guidelines of the Institutional Review Board of the University of Connecticut Health (IRB protocol 20-043-1). Patients referred to our clinic for endodontic treatment were initially screened based on the referral letters, radiographs and eligibility according to inclusion and exclusion criteria.

Inclusion criteria

1. Patients older than 18 years of age, both sexes and all ethnic groups.
2. Appropriate communication ability.
3. At least one tooth referred for RCT and two nearby normal teeth (no pain, no deep caries and no periapical lesion radiographically).
4. Affected teeth are endodontically involved and diagnosed with pulpitis or pulp necrosis.

Exclusion criteria

1. Porcelain-crowned teeth, which make cold or EPT tests less reliable or challenging.
2. Patients younger than 18 years.
3. Pregnant patients.
4. Patients with profound anxiety determined as Corah's scale equal or greater than 15.
5. Patients who currently take medications with anticholinergic side effects affecting skin conductance.
6. Patients who received prior sympathectomy procedures such as for hyperhidrosis treatment.
7. Patients with a diagnosis of Raynaud's syndrome which results in poor circulation of hands and may affect EDA detection.
8. Patients with contraindications to anaesthesia used in this study (2% lidocaine with 1:100 000 epinephrine and 4% septocaine with 1:100 000 epinephrine).

Corah's Dental Anxiety Scale is a four-question survey with five possible answers for the patient to select (Corah, 1969). Each answer has a score and the total score reflects patient anxiety. Scores between 15 and 20 suggest severe anxiety and possibly dental phobia. Due to the potential that anxiety can affect the EDA readings, we excluded patients with severe dental anxiety.

We provided consent and HIPAA forms to the eligible participants for review and signing. In this study, we recruited a total of 53 subjects for Aim 1 and 14 subjects for Aim 2. EDA data from cold test from four subjects (14 teeth) and EPT testing from two subjects (8 teeth) were excluded from analyses because they were considered EDA nonresponders. There were no TVSymp signals induced in normal and affected teeth in these participants. Demographic data are presented in the Results Section. Figure 1 shows a flow chart of the experimental design.

Power analysis to estimate sample size

We consulted a statistician to determine the sample size prior to data collection (Department of Statistics at the University of Connecticut). The sample size for the Pearson correlation test between TVSymp and VAS in Aim 2 is based on the one-sided hypothesis test (the population

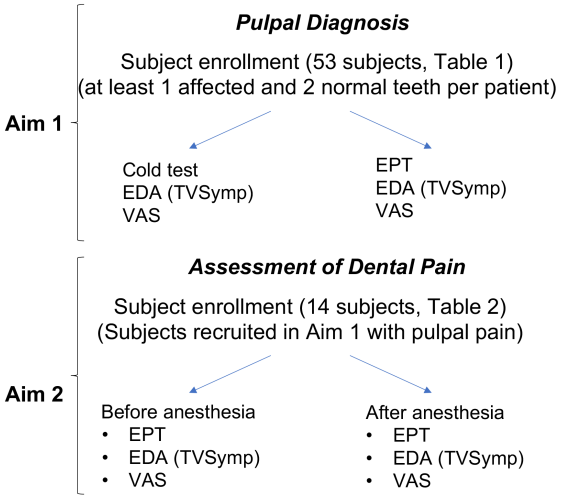

FIGURE 1 Flowchart summarizing the experimental design.

correlation coefficient under the null hypothesis is less than that of the alternative hypothesis) with a significance level of 0.05 and 80% power and a medium-effect size of 0.3 using G*Power (Faul et al., 2009). The sample sizes (n) are 67, 62, 54, 44, 34, 23, 13 and 3, respectively, corresponding to the population correlation coefficient under the null hypothesis to be 0.0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6 and 0.7. Approximately 60% of patients who require RCT in our clinic are diagnosed with symptomatic irreversible pulpitis. Thus, the sample size n for Aim 1 is estimated as the sample size of Aim 2 divided by 0.6. We obtained statistically significant differences in pain perception indicated by TVSymp and VAS before and after local anaesthesia from 14 subjects in Aim 2. Despite the impact of COVID-19, we were able to enrol 53 subjects for Aim 1 which was more than the estimated sample size number of 24 (14/0.6 = 23.33).

EDA recording during cold and EPT tests

We examined all patients in a room designated for research subject recruitment. EDA electrodes were placed on the index and middle fingers of patients and connected to the EDA recording device and signal digitizer (GSR AMP and PowerLab; ADInstruments) operated by a laptop computer (Figure 2a). Detailed steps of the EDA setup are shown in the Video S1. Patients were placed in a comfortable supine position. During this time, instructions for cold test and EPT were provided to the patients and all their questions were answered. EDA activity was recorded for at least 2 min to establish a baseline level and recordings continued during cold and EPT tests on the diseased and at least two nearby normal teeth. In addition, sham cold and EPT tests in normal teeth were performed and EDA signals were recorded. For the sham cold test, we sprayed Endo-ice but contacted the tooth surface with a dry cotton pellet only. For the sham EPT, we placed the probe on a tooth surface but used the tester without a battery. For all procedures, we instructed patients to stay stable and conducted the tests in a quiet environment to minimize EDA signals elicited by patient movement and unspecific background noise.

Cold testing was performed by applying an Endo-ice (1,1,1,2 tetrafluoroethane) refrigerant spray (Coltene, USA) to a cotton pellet, which was used to touch the buccal surface of the tooth. Patients were asked to raise their hand when they felt the stimulus, labelled as the starting point, and lower their hand once they no longer felt the sensation, labelled as the ending point of EDA recording of this test. Cold test results were recorded and categorized as (1) no response (−); (2) positive sensation (+) and (3) intensive response (++ ~ +++, with or without lingering pain). Exemplary EDA signals of each category of cold test are shown in Figure 2b.

Electric pulp testing was performed using a Kerr Vitality Scanner (SybroEndo). Toothpaste as a conductance medium was placed between the metal probe and the buccal surface of the tested tooth. Patients were asked to complete the circuit by holding the probe until a sensation was felt, at which point patients were asked to release the probe. The time-point, when the patient completed the EPT circuit, was labelled as the starting point and the time-point when the patient released the probe was labelled as the ending point. EPT results were dichotomized into 80/80 (=80, no sensation) or <80 (sensation). Exemplary EDA signals for EPT tests are shown in Figure 2c. The patient's VAS score was recorded after each stimulus.

Collected data include the patient's age, sex, race, ethnicity, anxiety level, testing time (AM or PM), periapical radiographs, cold and EPT tests performed, raw EDA signals, VAS and final pulpal diagnosis confirmed after accessing the pulp.

Record of EDA signals elicited by EPT before and after local anaesthesia

Patients who participated in endodontic diagnostic tests (Aim 1) and were diagnosed with symptomatic irreversible pulpitis (cold test: ++ or +++ with lingering pain; EPT test: +) and had agreed to receive endodontic therapy in our clinic were enrolled for assessment of dental pain before and after local anaesthesia in Aim 2. Patients with contraindications to local anaesthesia (2% lidocaine with 1:100 000 epinephrine and 4% septocaine with 1:100 000 epinephrine) were excluded.

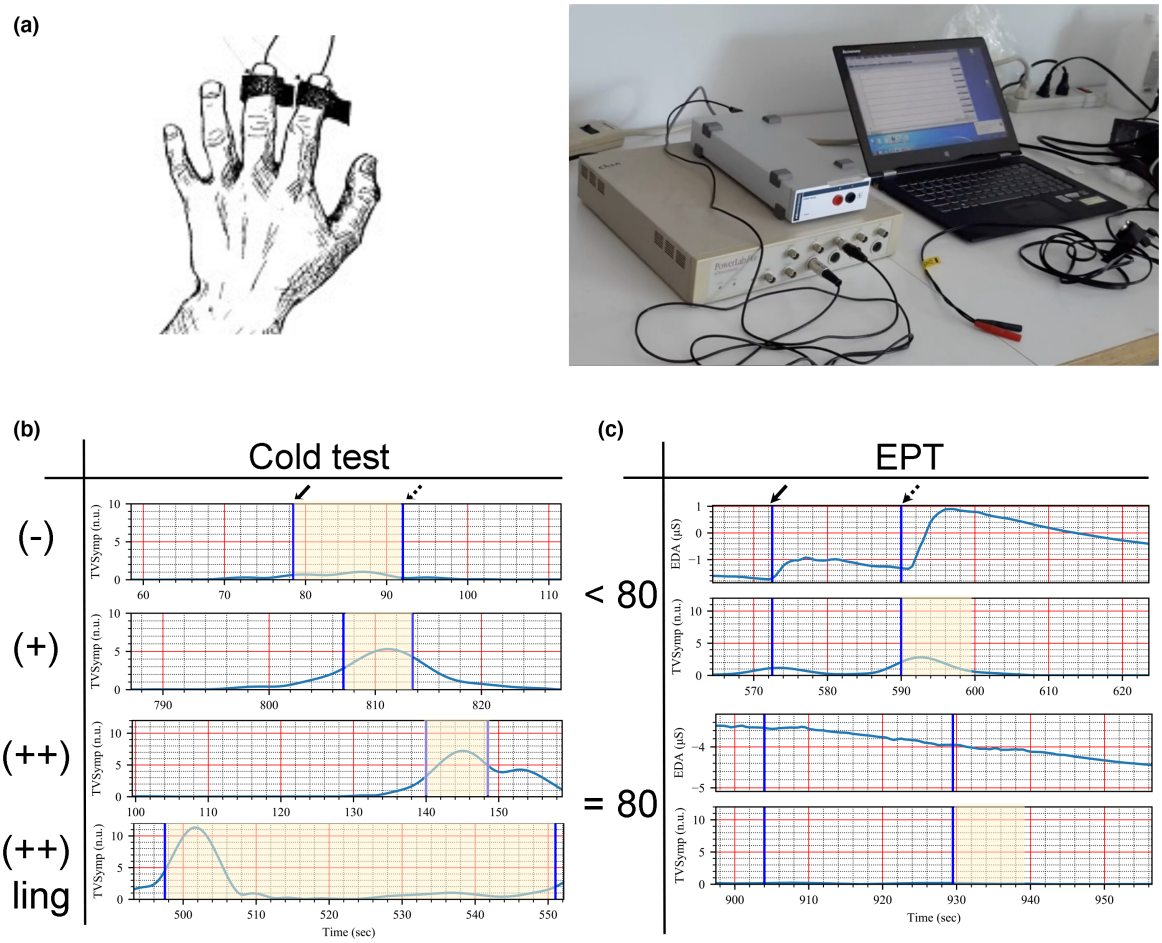

FIGURE 2 (a) Electrodermal activity (EDA) electrode placement on fingers (left panel) and EDA devices (right panel) including Galvanic Skin Response (GSR) Amplifier (top left), PowerLab (bottom left) and laptop; (b) exemplary time-varying index of sympathetic activity (TVSymp) signals elicited by cold test. From top to bottom are representative TVSymp signals for testing results being negative (−), positive (+) and intense positive with or without lingering pain (++, ++ ling). The solid arrow indicates the labelled starting point and dashed arrow indicates the labelled ending point. Light yellow indicates the time period used for data analysis. (c) Exemplary raw EDA data and TVSymp signals elicited by electric pulp testing (EPT). Representative images for testing results being <80 (top panels) and =80 (bottom panels).

Pre-anaesthesia VAS (VAS-pre) and TVSymp before anaesthesia (TVSymp-pre) were recorded previously as Aim 1.

Patients with a mandibular tooth needing treatment were given the following for anaesthesia: one carpule (1.7 ml) of 2% lidocaine with 1:100 000 epinephrine for inferior alveolar nerve block with 0.5 carpule (0.85 ml) of 4% septocaine with 1:100 000 epinephrine for buccal infiltration. Patients needing treatment of a maxillary tooth were given one carpule (1.7 ml) of 2% lidocaine or 4% septocaine with 1:100 000 epinephrine as maxillary infiltration.

Patients were assessed for the traditional signs of numbness, which included the lack of sensation to probing the gingiva around the tooth with a sharp explorer and signs of lip and tongue numbness. Patients who failed to report these signs after 15 minutes were given a single attempt of one additional carpule of anaesthesia. If patients still reported no signs following the additional anaesthesia, they were considered to have local anaesthesia failure and were dropped from the study. Once the patient exhibited the traditional signs of numbness, the TVSymp after anaesthesia (TVSymp-post) was then recorded under the stimulation of EPT. RCT was started in patients who reported numbness by the traditional signs and when the EPT output read 80/80. Immediately after the treatment, patients rated their pain intensity during the treatment on the VAS (VAS-post).

Data analysis

The collected and de-identified raw EDA data were processed and converted to TVSymp using Python 3.6. The

maximum signals of TVSymp and peak numbers of TVSymp from the cold test and the mean signals of TVSymp from EPT were calculated by Python 3.6. TVSymp was derived using a high-pass filter (0.01 Hz), variable frequency complex demodulation and the Hilbert transformation to evaluate signals in the frequency power range from 0.08 to 0.24 Hz, which is the frequency most associated with sympathetic activity (Posada-Quintero, Florian, Orjuela-Canon, Aljama-Corrales, et al., 2016; Posada-Quintero, Florian, Orjuela-Canon, & Chon, 2016). To compare TVSymp between test results of cold (i.e. negative vs. positive (+) vs. intense positive (++ or +++) with or without lingering pain), Kruskal–Wallis one-way ANOVA followed by Dunn's test was performed for multiple comparisons. To compare TVSymp signals between teeth reporting positive and negative EPT results (i.e. <80 vs. =80) and self-reported VAS, the Mann–Whitney *U* test was performed as these data were nonnormally distributed. To compare paired groups, paired *t*-test and the Wilcoxon signed-rank test were used for normally and nonnormally distributed data respectively. Normal and nonnormal distribution were determined by the Kolmogorov–Smirnov test. As TVSymp features and VAS were nonnormally distributed, Spearman's rank correlation coefficient assays were performed to analyse the correlation between TVSymp features and VAS scores. Statistical analysis was performed by Python 3.6 and its Scikit-*post hoc* library.

RESULTS

Characteristics of the recruited subjects and teeth in Aim 1 are summarized in Table 1. We recruited 53 subjects with an almost equal representation of males and females. White participants were the most common, followed by Black/African Americans, Asians, Native Americans and others. There was a greater population of non-Hispanic or Latino subjects than Hispanic or Latino subjects. The average age of recruited subjects was 36.2 years with an age range 19–72 years. Most of the study participants had mild-to-moderate anxiety. Twenty-six subjects were tested in the morning (AM) and 27 subjects were testing in the afternoon (PM). The most commonly tested teeth were premolars, followed by molars and anterior teeth. The most frequent diagnosis was pulpal necrosis, followed by symptomatic irreversible pulpitis and others.

To test the feasibility of using EDA as a complementary tool for cold test and EPT, EDA recordings of normal teeth with and without stimuli by cold or electric current were compared. For the cold test, the maximum level of TVSymp was determined within the time period between the starting and ending points. For the EPT testing, the mean value of TVSymp signal collected 10 seconds after the ending point was calculated. These differences were because the labelled ending point in cold test was when patient's sensation went away completely, whereas in EPT, the labelled ending point was when the patient released the metal probe, which was the beginning of patient's sensation. For EPT, we collected 10-second EDA signals because TVSymp signals rise instantaneously after the ending point and drop within 10 seconds in most cases (data not shown). Our results showed that normal teeth that received either cold test or EPT exhibited significantly higher TVSymp signals compared to teeth that received sham tests (Figure 3). In normal teeth, the VAS scores reported by patients after cold stimulus were significantly higher than after EPT. The median VAS for cold was 6 with a

TABLE 1 Characteristics of recruited subjects and teeth in Aim 1

Variable	*N*	%
Sex		
Male	26	49%
Female	27	51%
Race		
White	32	60%
African Americans	13	24.5%
Asians	2	3.7%
Native Americans	3	5.6%
Other	3	5.6%
Ethnicity		
Hispanic/Latino	22	41.5%
Non-Hispanic/Latino	31	58.5%
Anxiety level		
Mild (Corah's score < 9)	40	75.5%
Moderate (9–12)	10	18.8%
High (13–14)	3	5.6%
Testing time		
AM	26	49%
PM	27	51%
Tooth type		
Anterior teeth	42	22.2%
Premolars	87	46%
Molars	60	31.7%
Diagnosis (Affected teeth)		
Symptomatic irreversible pulpitis	21	32.3%
Asymptomatic irreversible pulpitis	3	4.6%
Partial necrosis	10	15.3%
Necrosis	31	47.7%

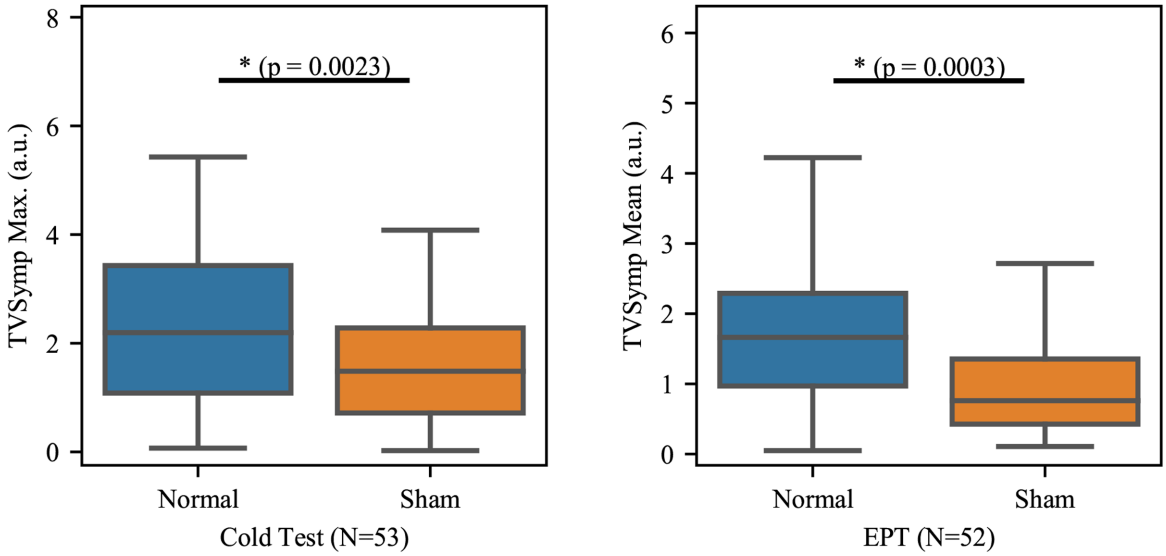

FIGURE 3 Induced time-varying index of sympathetic activity (TVSymp) signals by cold test (left panel) and electric pulp testing (EPT) (right panel) for teeth with normal pulp in comparison to the sham tests performed on the same teeth. Box plots show the median, minimum and maximum values, and the first and third quartiles. *p Value indicates a significant difference by paired t-test and the Wilcoxon signed-rank test for cold and EPT testing, respectively. N indicates the number of teeth being tested and analysed of 49 subjects for cold test and 51 subjects for EPT. Some subjects received two sham tests.

range 1–10 and for EPT the median VAS was 3 with a range 1–8 ($p < .001$ by Mann–Whitney U test).

We next determined TVSymp signals of teeth categorized by responses to cold, including the negative group (no response to cold indicates necrotic pulp), the positive group (positive but mild sensation indicates normal pulp) and the positive lingering group (intensive response to cold with or without lingering pain indicates reversible or irreversible pulpitis). TVSymp signals were statistically significantly increased in positive and positive lingering groups than in the negative group (Figure 4a). The average signals of TVSymp stimulated by cold in vital teeth were 2.1 ± 0.64 (mean ± SD)-fold increased compared to signals in necrotic teeth. The positive lingering group showed a trend of increased TVSymp amplitude but did not reach a statistically significant difference when compared to the positive group. The lack of a significant difference may be due to the small sample size in the positive lingering group. Interestingly, TVSymp peak numbers were significantly increased in teeth with a strong response to cold compared with teeth with mild sensation in the positive group (Figure 4b). The mean of TVSymp signals of teeth examined by EPT was calculated and teeth were categorized into groups of EPT < 80, indicating vital pulp, and EPT = 80, suggesting necrotic pulp. Teeth with vital pulp showed significantly increased TVSymp compared to necrotic pulp (Figure 4c). VAS scores of teeth (including both normal and affected teeth) that were responding electrodermally to cold and EPT and reported VAS score > 0 were compared. VAS scores of cold tests were significantly higher than EPT, suggesting that patient had a stronger sensation stimulated by cold (Figure 4d). The average signals of TVSymp stimulated by EPT in vital teeth (EPT < 80) were 2.29 ± 0.81 (mean ± SD)-fold increased compared to signals in necrotic teeth (EPT = 80). Spearman correlation coefficient analysis showed that TVSymp signals were moderately correlated with VAS reported after the cold test ($r = .38$) and only weakly correlated with the VAS score reported after EPT testing ($r = .24$). These data suggest that automated measurement for TVSymp does not correlate well with the subjective VAS pain metric.

For our second aim, we investigated the changes in EDA signals before and after local anaesthesia to assess whether EDA signals reflect a reduction in dental pain after anaesthesia. Patients recruited for this part of the study had at least one tooth diagnosed as symptomatic irreversible pulpitis. Pre- and post-anaesthesia TVSymp and VAS scores as a result of EPT stimulation of the affected tooth were recorded. Post-anaesthesia tests were performed after patients reported traditional signs of anaesthetic success including lack of sensation to probing around the affected tooth with a sharp explorer, lip and tongue numbness and negative EPT results.

The characteristics of the 14 subjects recruited and affected teeth for Aim 2 are summarized in Table 2. More females were recruited than males. White subjects and Black/African Americans were the most common racial groups. The average age of recruited subjects was 34.9 years with an age range 19–72 years. Eight subjects had zero-to-mild anxiety, followed by four subjects with moderate anxiety and two subjects with high anxiety. No differences in ethnicity and timing of testing. Molars were

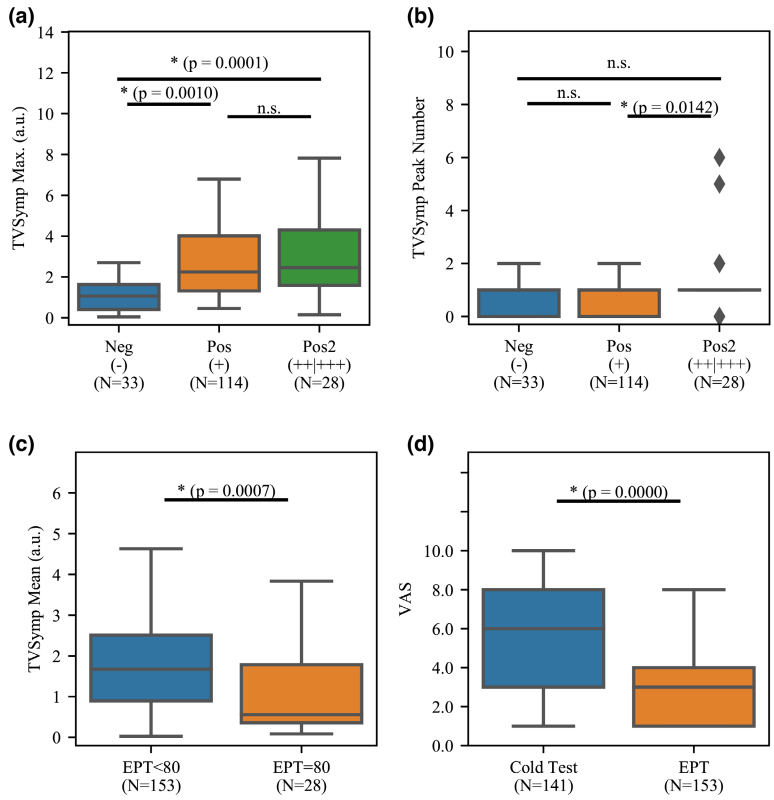

FIGURE 4 Quantitative measurements of time-varying index of sympathetic activity (TVSymp) signals and self-reported visual analogue scale (VAS) scores in patients receiving cold test and electric pulp testing (EPT). (a) TVSymp signals of teeth with necrotic pulp (blue) were significantly lower than in teeth with normal (orange) or inflamed (green) pulp. Neg (−): negative response to cold; Pos (+): positive response with mild sensation to cold; Pos2 (++/+++): intense response to cold with or without lingering pain. *p Values indicate significant difference analysed by Kruskal–Wallis one-way ANOVA followed by Dunn's test for multiple comparisons. (b) TVSymp peak numbers were significantly different between Pos (+) and Pos2 (++/+++) groups. (c) Averaged TVSymp signals 10 seconds after the labelled ending point of EPT testing show significantly increased TVSymp in teeth with EPT < 80. Statistical analysis was performed by Mann–Whitney U test. (d) VAS scores were significantly higher in cold tests than EPTs shown by Mann–Whitney U test. Only VAS scores > 0 were included in this analysis. N indicates the number of teeth being tested and analysed.

the most commonly treated teeth. Most of the patients were anaesthetized with a combination of 2% lidocaine and 4% septocaine.

Pre-anaesthesia TVSymp levels were significantly higher than those recorded after local anaesthesia (TVSymp-post) (Figure 5a). Whilst the majority of cases showed a reduction in VAS post-treatment (VAS-post), two subjects reported increased VAS and experienced increased pain during RCT treatment (Figure 5b) and did not have an observable reduction in the levels of TVSymp-post (Figure 5a). The efficacies of different anaesthesia were not compared due to small sample size.

Medians and interquartile ranges for each group in Figures 3–5 are presented in Table S1.

DISCUSSION

In this study, we explored the potential use of EDA in endodontics to quantify the sensation elicited by endodontic diagnostic tests and to assess the individual level of pulpal pain. The first step of our work was to detect changes in EDA signals between sham tests (baselines) and real stimuli (cold test or EPT) in normal teeth. Pooled data showed that EDA signals induced by stimulation are significantly higher than the baseline levels despite a wide range of variation amongst individuals. EDA signals are consistently induced by cold and EPT tests in normal pulp within a subject. Based on the results, it is essential to record EDA signals of sham tests (baseline) in each individual and compare the signals of normal and affected teeth in this individual. It is not feasible to define and apply a range of TVSymp values representing EDA signals at baseline levels or in normal or diseased pulp to all patients because the perception to thermal and electric stimulus or pain is a complicated patient-specific process and involves multiple factors that include demographic, physiological, psychological, sociocultural factors, etc.

Several studies have shown differences between males and females in EDA responsivity, with females showing

TABLE 2 Characteristics of recruited subjects and teeth in Aim 2

Variable	*N*	%
Sex		
Male	9	64%
Female	5	36%
Race		
White	10	71.4%
African Americans	3	21.4%
Other	1	7.1%
Ethnicity		
Hispanic/Latino	8	57.1%
Non-Hispanic/Latino	6	42.8%
Anxiety level		
Mild (Corah's score < 9)	8	57.1%
Moderate (9–12)	4	28.6%
High (13–14)	2	14.2%
Testing time		
AM	8	57.1%
PM	6	42.8%
Tooth type		
Anterior teeth	0	0%
Premolars	4	28.6%
Molars	10	71.4%
Anaesthesia		
2% Lidocaine with 1:100 k epi.	2	14.2%
4% Septocaine with 1:100 k epi.	2	14.2%
Both 2% lidocaine and 4% septocaine	10	71.4%

higher values and larger variability (Fedato et al., 2019; Kong et al., 2021; Venables & Mitchell, 1996). Sex differences are due to biological or cultural influences on the cognitive process and are independent of a smaller hand size in females (Fedato et al., 2020). Age and testing time are variables on their own or in interaction with other variables in EDA measurements. Older healthy adults (70–80 years) have lower EDA responses than younger adults (20–30 years) (Gavazzeni et al., 2008). There is a significant dependence on EDA responses and the time of the day in females but not in males. Only in females is the skin conductance level significantly higher in the morning in the cool season and afternoon in the hot season (Venables & Mitchell, 1996). External temperature and humidity may also influence EDA results but are less clear (Fisher & Winkel, 1979; Venables & Mitchell, 1996). In our study, all participants were tested in the same room with constant temperature and humidity. Our results showed that sex, race and time of day of testing do not significantly impact the EDA response to stimuli. The lack of significance from the effect of these factors may be due to the small sample size of this study. However, it was observed that in normal teeth, Hispanics/Latinos show a significantly higher TVSymp amplitude and VAS score to EPT testing ($p < .05$, Mann–Whitney U test) in comparison to non-Hispanic/Latino participants. Our and other studies consistently support that ethnicity may influence pain perceptions, leading to disparities in pain management (Bonham, 2001; Green et al., 2003; Ng et al., 1996). These data underscore the importance of comprehensive pain research with objective metrics and further development of personalized medicine approaches for pain control. Although it is critical to take these factors into account when conducting studies using EDA measurements, their practical importance is limited in our study as we compared EDA signals within the same individuals.

This study defined general patterns of TVSymp signals corresponding to the results of diagnostic tests. The TVSymp amplitude of normal pulp and teeth that had an intense response to cold is above baseline and higher than teeth with necrotic pulp. For EPT tests, we identified the correlation of limited TVSymp signals to necrotic pulp and increased amplitude of TVSymp (higher than baseline levels) to the vital pulp. This methodology, however, is probably over-simplified and the analysed TVSymp data did not always match the final diagnosis. It was observed that 88% and 93.2% of necrotic teeth have low EDA, consistent with negative responses to cold and EPT testing respectively. These consistent measurements in vital teeth were reduced to 72% for the cold test and 70% for the EPT test. The increased inconsistency in vital teeth may be due to a large variation in pulpal status including normal, reversible pulpitis, irreversible pulpitis and even partial necrosis. The major confounding factor is dental anxiety and stress, which can provoke greater EDA responses during the testing period. EDA has been used to measure nociceptive pain as well as dental anxiety (Casap et al., 2008; Chen et al., 2014; Storm, 2008). Dental intervention is in general a stress-provoking situation. The fear, anxiety and perceived stress in the dental setting are particularly higher in children with a developmental disability (Pop-Jordanova et al., 2018; Shapiro, Melmed, et al., 2009). In this pilot study, we have excluded children and those with dental phobia evaluated by a Corah's anxiety scale to minimize the EDA confounding factors attributed to patient anxiety and stress. In spite of these efforts, we still observed some unspecific EDA signals, which are most likely contributed to patient anxiety and the anticipation of upcoming tests. Additionally, EDA artefacts can also be generated by excessive movement or adjustment of the device. If these artefacts remain in the signal, they can easily lead to misinterpretation and skew the data analysis. Our

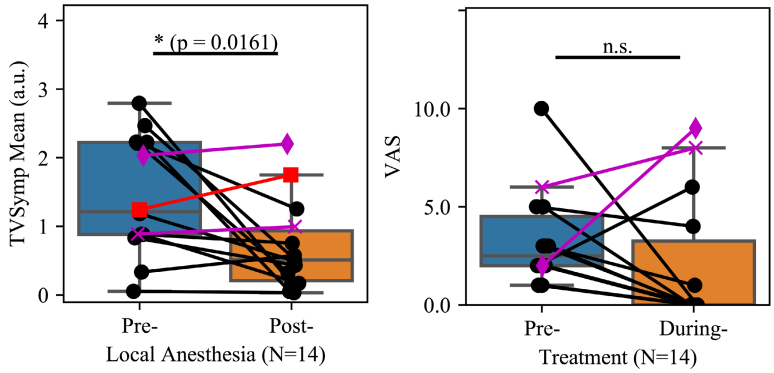

FIGURE 5 Box plots present time-varying index of sympathetic activity (TVSymp) signals measured before and after local anaesthesia (left panel) and visual analogue scale (VAS) scores reported before treatment and during treatment (right panel). Treatment was initiated after the detection of traditional numbing signs after local anaesthesia. Two subjects (labelled as magenta lines) who had increased pain during the treatment also displayed increased TVSymp signals, suggesting the failure of local anaesthesia. The subject labelled with a red line had increased TVSymp but decreased VAS score. Statistical analyses were performed by paired *t*-test (left panel) and Wilcoxon signed-rank test (right panel).

future work will focus on developing a machine-learning algorithm that can automatically and accurately detect specific EDA signals and distinguish these 'real' signals from artefacts.

To investigate whether EDA can assess pulpal pain, we determined TVSymp of preoperative pain and compared it to the signals measured after local anaesthesia. Successful anaesthesia was determined by traditional signs of numbness and EPT measurement (80/80). EPT has been shown to predict 73% anaesthetic success of teeth diagnosed with acute pulpitis and 100% of teeth with no preoperative pain (Dreven et al., 1987). Ten of 14 patients (71%) had successful anaesthesia as they did not experience any pain during the treatment based on self-reported VAS scores. Interestingly, the majority of patients also showed a reduction in TVSymp post-anaesthesia. Two patients who experienced increased pain (increased VAS score) during treatment also did not show reduced TVSymp after local anaesthesia. Although our sample size is small, this pilot study suggests that TVSymp may be a sensitive EDA parameter to assess dental pain. To improve the sensitivity and specificity of EDA in pain assessment, our future study will investigate whether other EDA features including the power spectral density, the phasic component and other time-varying indices of sympathetic activity outperform TVSymp in assessing dental pain. We will also evaluate whether TVSymp stimulated by cold test can better predict anaesthetic success than the EPT test. Cold testing has been shown to predict 88% anaesthetic success (Hsiao-Wu et al., 2007).

The sensation and description of pain are influenced by many factors including the personality of individuals, their past experience with painful events, age, culture, etc. Although pain is not a single sensation perceived as intensity, it has been agreed that intensity is the most clinically relevant dimension to pain assessment (Collins et al., 1997). To date, VAS is the most commonly used tool to evaluate different causes of pain and pain in different clinical settings (acute pain, chronic pain, postoperative pain and pain changes after analgesic administration). In our study, we used the 11-point numerical rating VAS scale (0–10), which may be less sensitive than the 100 mm VAS scale. However, the conventional 100 mm scale is not a linear phenomenon and it is difficult to determine which range of the 100 mm continuum corresponds to clinically relevant moderate pain, which may lead to difficulties in data interpretation (Collins et al., 1997; Hirschfeld & Zernikow, 2013). VAS has been shown valid and reliable for acute abdominal pain (Gallagher et al., 2002). In contrast, VAS is not recommended for patients with chronic musculoskeletal pain (Boonstra et al., 2008). We observed a moderate positive correlation between TVSymp and VAS scores of cold tests ($r = .38$) and a weak correlation of EPT tests ($r = .24$). It was noted that the VAS score of cold tests is significantly higher than the VAS of EPT tests (Figure 3d). A better correlation between TVSymp and VAS in cold tests may be related to the stronger sensation elicited by the cold test. Our data provide preliminary support for utilizing EDA signals as a physiomarker for dental pain. If proven, this will particularly benefit patients who are not able to accurately express their sensation of pain or not able to comprehend the VAS scale.

There are several clinical limitations in the application of EDA. A small percentage of the general population have no electrodermal response. The reason that healthy individuals produce very low or unmeasurable EDA activity, considered EDA nonresponders, is unknown (Alexandra Kredlow et al., 2017). The EDA nonresponders are those who gave no responses >0.05 μS to the six stimuli as defined by Venables &

Mitchell, 1996. Based on different study designs, nonresponders to intense stimuli ranged between 5% and 10% (Ohman, 1981; Venables & Mitchell, 1996). We encounter four and two subjects who were EDA nonresponders to cold and EPT stimuli. These nonresponders were excluded from data analysis in this study. The other limitation is the use of medications which can significantly affect the skin conductance levels and thus the EDA responsivity. Many common medications have anticholinergic side effects, like medications for allergies, common cold, insomnia, antipsychotics and antidepressants. It is sometimes impractical to omit prescribed medications even for a short period. Moreover, medical conditions or diseases that affect sweat production like sympathectomy and Raynaud's disease will also limit the use of EDA measurement.

CONCLUSION

This study explores the use of EDA elicited by routine pulpal diagnostic tests and assesses the changes to pain levels after the administration of local anaesthesia. The data analysis revealed significant differences in TVSymp between necrotic and vital pulp, suggesting that this new method can potentially serve as an adjunct to current diagnostic tests in endodontics. It also supports the potential use of TVSymp to predict anaesthetic success. However, more research is needed to distinguish real and unspecific background EDA signals. Future work in this area could lead to the development of quantitative and subjective measurements of dental pain to benefit patients who are unable to accurately express their pain sensations. This method will likely be useful to study the effectiveness of pain medication and monitor the use of opioids, such as after dental surgical procedures.

AUTHOR CONTRIBUTIONS

HT. T. and Y.K.: data collection, data analysis and interpretation, writing and revising the paper and final approval of the submitted version. A.T.: data collection and final approval of the submitted version. H. P-Q: study conception, data interpretation, revising the paper and final approval of the submitted version. K. C.: study conception, data interpretation, revising the paper and final approval to the submitted version. IP.C.: study conception and design, data collection, data interpretation, writing and revising the paper and final approval of the submitted version.

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CONFLICT OF INTEREST

K.C. is a founder of a start-up company Physiosense Technologies. Other authors deny any conflicts of interest related to this study.

DATA AVAILABILITY STATEMENT

Research data are not shared.

ETHICS STATEMENT

All human studies were in accordance with guidelines of the Institutional Review Board of the University of Connecticut Health (IRB protocol 20-043-1).

PATIENT CONSENT

We provided consent and HIPAA forms to the eligible participants for review and signing.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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