ORIGINAL ARTICLE

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Assessing smartphone-derived heart rate variability as an indicator of general and oral health: an exploratory study

Abstract

Objective: This study aimed to investigate the feasibility and effectiveness of using smartphone-derived heart rate variability (HRV) as a diagnostic tool for assessing both general and oral health conditions. **Methods:** An exploratory and cross-sectional study was conducted. HRV was recorded through smartphone photoplethysmography (PPG). Were searched associations between HRV and the American Society of Anesthesiologists (ASA) risk classification in dentistry, tooth loss (TL), dental maintenance and rehabilitation status (DMRS), and periodontal disease (PD). To confirm the reliability of signal acquisition pattern by PPG method via smartphone, heart rate (HR) was compared using four additional devices. **Results:** The HR derived from the smartphone demonstrated reliability comparable to traditional monitoring devices. Significant associations were found between higher HRV scores with better oral health outcomes. Smartphone-derived HRV was able to detect comorbidity with 68.3% of sensitivity and 61.5% of specificity. **Conclusion:** This study underscores the potential of smartphone-derived HRV as a complementary diagnostic tool for evaluating both general and oral health conditions. The findings reveal discernible associations between HRV and the ASA classification for risk in dentistry and with the studied oral health parameters. HR derived from smartphone is reliable when compared with traditional cardiac monitoring devices.

Keywords: Heart rate variability; Heart rate; Oral health; Periodontal disease; Tooth loss.

INTRODUCTION

Homeostasis and allostasis are regulated by efferent neurons of the autonomic nervous system (ANS), which control the function of effector organs. The ANS comprises two branches: the parasympathetic nervous system (PNS), primarily responsible for promoting vegetative activities like heart rate regulation, gut motility, and even mediating the inflammatory reflex through the cholinergic anti-inflammatory pathway. The second branch is the sympathetic nervous system (SNS), which upregulates effector organ function, such as increasing blood pressure through the release of catecholamines[1-4]. Heart rate variability (HRV) analysis relies on the RR time series, representing temporal differences between successive heartbeats intervals. These time intervals are derived from the sequence between successive fiducial points of R peaks of QRS complexes in the electrocardiogram (ECG) and reflect fluctuations in atrioventricular conduction. HRV mirrors ANS regulation over the heart, which is constantly modulated by respiration, blood pressure, and central autonomic network activity in the brain. Consequently, HRV measurements offer perspectives into the functioning of both branches of the ANS[1,2,5,6].

Statement of Clinical Relevance
This study explores smartphone-derived HRV as a potential diagnostic tool to assess general and oral health, examining its link to comorbidities and its role in risk evaluation and patient safety.

Variations in HRV patterns may serve as an early indicator of health disruptions. High HRV typically signifies robust adaptation, reflecting efficient ANS functioning in healthy individuals. In contrast, low

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HRV often signals abnormal ANS adaptation, suggesting potential physiological dysregulation in the patient[2,6,7]. Decreased HRV has been associated with an unfavorable prognosis or is considered a biological marker across multiple health conditions, including cardiovascular diseases such as ventricular tachycardia, arterial hypertension, hypertrophic cardiomyopathy, and sudden cardiac death. Additionally, conditions like intrauterine growth retardation in fetuses, geriatric syndromes including cognitive disorders and neurodegenerative diseases, affective disorders like depression, post-traumatic stress disorder, pain, diabetes, systemic inflammation, smoking, and physiological factors such as age, fitness level, cognition, and stress have been linked to diminished HRV[2,4-9].

Smartphones are equipped with powerful processors, AI-powered operating systems and applications, as well as advanced sensors like high-resolution cameras, enabling photoplethysmography (PPG), which is an optical technique[10]. PPG-based systems utilize the index finger on the smartphone's built-in standard camera while keeping the LED flashlight turned on, allowing non-invasive measurement of many physiological parameters, including blood volume, blood pressure, heart rate, heart rate rhythm, HRV, and ECG. Nowadays it has been built into almost every wearable device on the market, and HRV can be conveniently recorded and analyzed (Li)6. The peak-to-peak interval of PPG is known to be highly correlated with the RR interval of ECG and meta-analysis study showed no statistical difference between the measurement of heart rate by PPG-based smartphone and other validated methods; however, the presence of artifact due to movement during signal acquisition in this method is still an open issue[6,11-14]. ECG-based systems utilizing PPG technology may offer a convenient, affordable, and accessible solution for monitoring health parameters[6,13,14].

There is a growing body of evidence suggesting that common oral conditions such as periodontitis, caries, apical periodontitis, tooth loss, and masticatory dysfunction may contribute to or is associated with various systemic diseases, particularly cardiovascular and cerebrovascular disorders, extending to an elevated risk of cancer and mortality[15-20]. Given the intricate interconnection of the autonomic nervous system with systemic health, it stands to reason that alterations in HRV patterns could potentially serve as a marker for detecting underlying systemic health issues in individuals with poor oral health. Interestingly, this context has not yet been thoroughly explored in the current literature[9], presenting an avenue for further investigation into the link between oral health status, autonomic nervous system function, and overall systemic health.

The objective of this exploratory study is to investigate the feasibility and effectiveness of using smartphone-derived HRV as a diagnostic tool for assessing both general and oral health conditions, verifying the potential associations with the ASA risk classification in dentistry, tooth loss, oral rehabilitation status, and periodontal disease. The hypothesis is that HRV may demonstrate discernible associations with the ASA classification for risk in dentistry, as well as with the explored oral health conditions. Confirmation of the hypothesis in clinical terms would also bring advancement in understanding the interrelations between oral and systemic health.

MATERIALS AND METHODS

Study design and sample characteristics

This study was classified as observational, cross-sectional, prospective, and exploratory. It underwent review by the State University of Ponta Grossa Committee for Human Ethics Research and was approved under the number 5.715.941. Informed consent was obtained from all study participants. The inclusion criteria encompassed a sample that was conveniently sourced; however, the patients were selected randomly. Specifically, it comprised a group of volunteers aged 18 years or older who were seeking consultation or dental treatment at the dental university clinics. Exclusion criteria encompassed patients with know heart diseases which may interfere with rhythm beats such as pacemakers, diagnosed arrhythmias, or anxiety-induced arrhythmias, as well as those with advanced mental illness or cognitive limitations impairing comprehension of the research terms and questionnaires, and patients who declined to participate in the research. Sociodemographic characteristics of the patients were collected through an interview questionnaire.

The sample size was calculated using G*Power (version 3.1.9.7), considering the a priori required sample size for correlation analysis with the following parameters: two-tailed test; effect size $|\rho|=0.3$; α probability error=0.05; and power (1-β error probability)=0.9. The minimum required sample size was determined to be 109 observations. To account for potential losses, an additional 5% was included, resulting in 115 observations.

Sociodemographic, general health condition and risk evaluation by the American Society of Anesthesiologists Classification (ASA)

Sociodemographic and medical information, such as gender, age, body mass index (BMI), education level, smoking status, medication usage, were initially collected through an anamnesis interview. Subsequently, a modified ASA classification system questionnaire for dentistry, the European Medical Risk Related History (EMRRH), was administered. This questionnaire does not include the ASA V category since patients in such conditions would likely be too unwell to attend a dental appointment. The primary purpose of the EMRRH is to document medical conditions and comorbidities that could impact dental treatment and evaluate the level of associated medical risk[21]. According to the questionnaire, patients are classified as ASA I for healthy individuals, ASA II for those with mild to moderate systemic diseases that do not significantly affect daily life, ASA III for patients with severe systemic diseases limiting activity but not incapacitating, and ASA IV for patients with severe systemic diseases posing a constant threat to life[21].

Oral health condition

The clinical oral exam was conducted by two trained and calibrated postgraduate examiners, and any uncertainties were addressed by an experienced oral medicine professor.

(a) Tooth loss (TL) or the number of remaining teeth (NRT) was determined by counting all remaining teeth, including third molars. Residual roots, when present without a crown, were not included in the count for NRT[22].

(b) The Dental Maintenance and Rehabilitation Status (DMRS) was classified based on the preserved number of teeth and the rehabilitation status of the maxilla and mandible individually, as follows:

- (0) for being toothless without any prosthesis;
- (1) for being toothless rehabilitated with a total denture;
- (2) for being partially dentate without any prosthesis;
- (3) for being partially dentate with a removable partial prosthesis;
- (4) for being partially dentate with dental implants or fixed prosthesis (still missing many teeth);
- (5) for having a preserved oral condition due to the presence of most teeth and dental implants or fixed prosthesis; and
- (6) for having a preserved oral condition due to the presence of all teeth (excluding third molars).

An index was computed to evaluate the preserved masticatory function, based on dental condition and rehabilitation, by summing the scores for the maxilla and mandible, resulting in an index ranging from 0 to 12. Higher scores indicate better-preserved dental condition and rehabilitation[22].

(c) Periodontal disease (PerD) was classified as either the absence of evidence or the presence of periodontitis, determined by meeting the following criteria: the presence of ≥2 interproximal sites with clinical attachment loss (AL) ≥3 mm, and ≥2 interproximal sites with probing depth (PD) measurements ≥4 mm (not on the same tooth), or one site with PD ≥5 mm (stage I or superior)[23].

Heart rate comparability and heart rate variability

Heart rate variability (HRV) was recorded through the Pulse HRV app on an Android® operating system smartphone (Samsung Galaxy Series®). This app utilizes the smartphone's camera along with a light-emitting diode to apply photoplethysmography (PPG) technique, which detects changes in blood volume during the cardiac cycle. The software yields HR, HRV total score, and HRV classification, respiration-pulse coherence, providing detailed record data which are based on age, gender and recent physical activity. The app provides descriptions based on the time series, spectral analysis (shows the balance of the Autonomic Nervous System – ANS) and graphical such as; temporal difference between successive heartbeats (RR avg distribution), standard deviation of RR intervals (SDNN; normal-to-normal deviation of intervals measured between consecutive sinus beats), difference between RR intervals such as the root mean square of successive differences of RR intervals (RMSSD), Poincaré plot, power spectral density (PSD) plot, among others. To minimize artifacts, the patient's hand and finger were positioned in a supported rest position. Patients were instructed and monitored to maintain a consistent breathing rate, as indicated by the app, for one minute to ensure coherence during data collection.

To validate the heart rate readings and confirm the reliability pattern of the PPG method via smartphone, heart rate was also recorded using four additional devices: a multi-parameter cardiac monitor (Inmax12 Monitor, Instramed Co., Brazil), an automatic blood pressure monitor (Omron Dalian Co., China), a pulse oximeter (Realdox MD 300C4, Beijing Choice Co., China), and a handheld electrocardiogram (PC-80-B, Easy ECG Monitor, Shanghai Lishen Scientific Equipment Co., China).

Statistical procedures

The freeware JAMOVI software (JAMOVI project, 2023, Version 2.4.11.0) and the freeware BioEstat software (BioEstat 5.3, Ayres M.; Ayres DL; Santos AAS; Brazil), were employed to analyze the data through descriptive and inferential methods. A two-tailed probability of p≤0.05 was considered statistically significant. The variables were classified as continuous, ordinal, or nominal and the appropriate statistical tests were selected based on these characteristics, taking into account the normal or non-normal distribution of the variables and determined by the assumptions check tests. For heart rate (HR) agreement the analysis was used the Concordance Correlation Coefficient (CCC), Shieh Test of Agreement and Bland-Altman Statistics. The Screening Test was used to verify the sensitivity and specificity of the altered HRV (through classification app report) for detection of any comorbidity. The Receiver Operating Characteristics (ROC) Curve was use to find an optimized cut-off value of HRV in order to improve the sensitivity and specificity tests for detection comorbidities. Eventual missing data were treated by sample mean and outliers by winsoring. Lack of sensitive data were treated by case exclusion.

RESULTS

Sample characterization

The sample initially consisted of 114 patients undergoing dental care, with two of them being excluded. One (a 21-year-old patient) had a cardiac pacemaker, and the other (an 18-year-old patient) exhibited symptoms compatible with an anxiety disorder, leading to a condition resembling arrhythmia (palpitations), resulting in a total of 112 patients. Among the included patients, females represented 65.2% of the sample (73 cases). The age ranged from 19 to 86 years (mean of 38.3 years, SD±16.2). According to the BMI classification, 27.7% (31 patients) were classified as overweight and 15.2% (17) were obese patients. From this sample, 76.7% never smoked, 9.8% are ex-smokers while 13.5% were smokers. Healthy individuals (ASA I) represented 46.4% (52 patients) of the sample while patients with any comorbidity or with associated risk factor (ASA II or superior) detected were 53.6% (60) distributed as; ASA II 38.4% (43), ASA III 11.6% (13) and ASA IV 3.6% (4).

Heart rate comparability and smartphone-derived heart rate variability

To ensure the reliability of the HR readings for the smartphone, it was compared with four additional HR measurement devices, as shown in Table 1. The HRV app classification results indicate that 2.7% (3) of the patients were categorized as poor, while 17% (19) show room for improvement. Additionally, 43.8% (49) fall within the normal range, 32.1% (36) were classified as good, and 4.5% (5) of the patients were classified as excellent. The raw results for HRV obtained through the smartphone ranged from 11 to 140 (mean of 39.3; SD±22.3).

Smartphone-derived heart rate variability and sociodemographic factors

HRV showed a negative correlation with increasing age (Spearman's test, 2-tailed, rs -.26, p= .005), and no additional significant differences were observed with any other sociodemographic factors.

Table 1. Heart rate readings for the smartphone and compared with four additional heart rate measurements devices followed by the Concordance Correlation Coefficient, Shieh Test of Agreement and Bland-Altman Statistics (t-statistic and p-value).

HR Reading Devices	Mean	Median	SD	SD-HR/CCC	SD-HR Shieh's Test	SD-HR Bland-Altman Stat.
Smartphone-derived (SD-HR)	76.3	73.0	12.4	-	-	-
Handheld Electrocardiogram	77.0	75.0	12.3	0.63	NS	t=-0.7/p=0.5*
Automatic Blood Pressure Monitor	77.1	75.0	11.9	0.69	NS	t=-0.8/p=0.4*
Pulse Oximeter	76.3	73.0	11.9	0.66	NS	t=0.006/p=1*
Multi-Parameter Cardiac Monitor	76.7	75.0	11.3	0.77	NS	t=-0.5/p=0.6*

*The absence of a significant difference or bias between the two measurement methods indicates that they are in good agreement and can be used interchangeably for measurement purposes.

SD: standard deviation; HR: Heart rate; CCC: Concordance Correlation Coefficient; NS: Not significant differences observed. There is no systematic difference between the two methods.

Smartphone-derived heart rate variability and American Society of Anesthesiologists risk classification

HRV showed a negative correlation with increasing ASA classification (Spearman's test, 2-tailed, rs -.25, p= .008). Patients classified as healthy (ASA I) had a mean HRV index of 46.2 points, while patients with comorbidities (ASA II or higher) had mean HRV indices of 33.3 (Mann-Whitney test, p= .002).

Using HRV as a straightforward test to detect any comorbidity (ASA I *versus* ASA II or higher) through the Screening Test, with likely presence of disease indicating a positive test and unlikely presence of disease indicating a negative test, yielded the following results (as classified by the smartphone algorithm):

- Sensitivity = 26.67% (proportion of sick individuals whose test is positive).
- Specificity = 88.46% (proportion of individuals without the disease whose test is negative).
- False-positives (Type I Error) = 11.54% (proportion of healthy individuals whose test is positive). False-negatives (Type II Error) = 73.33% (proportion of sick individuals whose test is negative).
- Positive predictive value = 72.73% (probability of an individual having the disease when the test is positive). Negative predictive value = 51.11% (probability of an individual not having the disease when the test is negative).
- Accuracy = 55.35% (measure of a test's exactness).
- +LR (Positive Likelihood Ratio) = 2.31 (chance of disease when the test is positive). LR (Negative Likelihood Ratio) = 0.83 (chance of disease when the test is negative).

When exploring the raw values of HRV to find the best cutoff point for classifying individuals with any comorbidity, the Receiver Operating Characteristics (ROC) Curve was used, indicating a cutoff value of 35 points for HRV. With this cutoff value, the Screening Test showed an improvement for the sensitivity test (Sensitivity = 68.3%) and a decrease of the specificity test (Specificity = 61.5%).

Heart rate variability and oral condition

The number of natural remaining teeth ranged from complete edentulous patients to patients with 32 teeth (Mean 24±8). When analyzed in isolation, better scores of HRV showed a positive correlation with the number of remaining teeth in the mouth (Spearman's test, 2-tail, rs .26, p= .005).

Having a diagnosis of periodontal disease (PerD; 30 patients or 26.8%), compared to those who do not presented it, showed an association with HRV values (PerD, HRV 32.5/no-PerD, HRV 41.8; Mann-Whitney test, p= .018).

The Dental Maintenance and Rehabilitation Status (DMRS) mean score was 9.5 (SD±3.4) and this condition indicated that the better preserved or rehabilitated the masticatory function, the better was the HRV (Spearman's test, 2-tail, rs .22, p= .02). Individuals with any comorbidity (ASA II or superior) scored significantly lower values for DMRS (Healthy, 10.9; Any comorbidity, 8.2; Mann-Whitney Test, p< .001). When DMRS was compared to HRV (using the cutoff value of 35 points), significant differences were also observed, with worse HRV readings associated with lower DMRS scores (HRV>35: 10.1; HRV<35: 8.8; Mann-Whitney Test, p = .03).

DISCUSSION

Heart rate variability (HRV) has emerged as a robust biological marker for assessing various diseases, providing a glimpse into the autonomic nervous system's regulation by the physiological functions. This makes HRV an interesting tool for patient monitoring, offering clinicians information into the overall health status of patients. In the past, obtaining ECG and consequently HRV data was costly and time-consuming due to the need for specialized equipment and expertise, however, nowadays, reliable ECG can be obtained easily from many devices including smartwatches and smartphones. The improvements of smartphone technology, specific applications for health monitoring and improvements in photoplethysmography (PPG) sensors have revolutionized the process of obtaining ECG which may offer a convenient and affordable means of collecting physiological data, thus providing promising method for patients further and deeper investigation or even facilitating remote health monitoring[1,5].

While HRV's utility in evaluating general health conditions is well-documented, its application in dentistry remains relatively unexplored, with only a few identified manuscripts in the literature[8,9,24-27]. The present study highlights the potential implications of HRV for risk assessment in dental settings, particularly in identifying patients at increased risk during procedures. By integrating HRV as a supplementary diagnostic tool in dentistry, clinicians can enhance their comprehension of patients' health profiles, facilitating more informed treatment decisions and ultimately improving patient safety in dental care. Although this study did not compare HRV between different validated methods, it focused on obtaining HRV via heart rate by utilizing software capable of detecting the sequence of intervals between successive heart peaks and generating real-time HRV data. Nonetheless, the study demonstrated that smartphone apps equipped with photoplethysmography technology can yield of HR measurements comparable to those obtained through established monitoring devices such as multi-parameter cardiac monitors with no statistical or systematic difference between the two methods. Heart rate and HRV represent distinct physiological parameters. While accurate heart rate measurements can suggest reliable signal acquisition, assessing HRV demands additional processing and analysis. It's worth noting that modern smartphones often possess the capacity for such comprehensive HRV analysis. This suggests that smartphone-based HRV monitoring holds potential as a reliable alternative for assessing autonomic nervous system function, offering convenience and accessibility without compromising accuracy.

The observed associations between HRV and the American Society of Anesthesiologists (ASA) classification for risk in dentistry suggest that HRV could serve as an indicator of overall health. While no studies in dentistry have explored this association before, a research in the medical field has observed similar correlations between disease severity or higher ASA grade and low HRV, indicating poor physiological reserve and heightened risk of hemodynamic instability[28]. However, conflicting findings exist, with a study also showing no significant associations between ASA grade and HRV[3].

This study demonstrated that HRV, with a cutoff value of 35 points, can effectively identify comorbidity or risk, regardless of its nature, with a sensitivity of 68.3% and specificity of 61.5%. These findings suggest that the test accurately detects comorbidity or a patient with increased risk in 68.3% of cases (true positives) while correctly excluding comorbidity or risk in 61.5% of cases (true negatives). These results highlight HRV's potential as an additional and fast screening tool in dentistry, going beyond standard assessments to provide comprehensive health evaluations. In instances where HRV indicates a heightened risk not detected during routine interviews, further examinations could be warranted. Despite its limitations, HRV assessment offers practical applications in dentistry, aiding clinicians in identifying patients requiring special considerations during dental procedures or additional health management strategies. Integrating HRV assessment into pre-treatment evaluations can refine risk assessment protocols, ultimately bolstering patient safety in dental practice.

Tooth loss has been a biological marker commonly associated with several systemic conditions[15-17] and it is often stemming from advanced periodontitis, reflects a culmination of poor oral health conditions in the life course of an individual[20] as well as several studies have similarly linked patients with periodontitis with cardiovascular and cerebrovascular diseases[18-20]. The progression of periodontitis often culminates in tooth loss, which subsequently impairs functional mastication. This impairment can lead to a decreased ability to properly chew tougher, more fibrous foods, consequently reducing the intake of essential fruits and vegetables. In compensatory response, individuals may resort to consuming more soft, processed foods, which are often lacking in nutritional value and may contribute to obesity and adverse health outcomes[29]. So, the mechanisms in which poor oral health is linked to several other systemic conditions may include different pathways and mechanisms such as oral microbiome dysbiosis, inflammatory pathways, pathogen-associated molecular patterns and damage-associated molecular patterns, pattern recognition receptors, entero-salivary nitrate-nitrite-nitric oxide pathway, endothelial dysfunction, epigenetic modifications and possibly others not fully identified[20]. The present study observed a link between tooth loss, presence of periodontitis and the Dental Maintenance and Rehabilitation Status with poor HRV measurements which also reflects a poor general health condition. This intricate relationship highlights the potential influence of oral health status such as chronic inflammation, pain and discomfort on autonomic nervous system function, which may in turn affect HRV patterns. However, it is important to note that the scope of this study does not allow for the inference of one factor over another or demonstration of a causal relationship between these factors; rather, it solely observes their associations.

One potential mechanism underlying the presence of periodontitis, supported by abundant evidence in current literature, involves the release of pro-inflammatory cytokines and acute-phase reactants from periodontal tissues into systemic circulation. This process can activate autonomic centers located in the brainstem, potentially leading to alterations in heart rate variability (HRV). Additionally, specific inflammatory mediators capable of crossing the blood-brain barrier (BBB) trigger the activation of the brain's resident immune cells within the central nervous system (CNS). This activation initiates a cascade of responses within the CNS, which may further influence autonomic nervous system function, ultimately contributing to changes in HRV. Impaired mastication resulting from tooth loss and compromised DMRS may disrupt sensory feedback to central autonomic centers, thereby affecting the balance of the autonomic nervous system (ANS) and potentially influencing HRV. Several studies have demonstrated associations between masticatory dysfunction, periodontitis, and tooth loss with cognitive decline and dementia[15-19,30]. Recently, a systematic review found a longitudinal association between HRV and cognition in adults[4] and the the central nervous system exerts profound control over ANS activity, with higher brain centers, such as the hypothalamus and brainstem, integrating sensory information and modulating autonomic responses. Investigating these mechanisms could provide a different view into the complex interplay between oral health and autonomic regulation, including HRV dynamics. Moreover, it's important to consider that these health conditions may also be influenced by sociodemographic and cultural factors, income levels, access to healthcare services, age advancement, smoking habits, lifestyle, physical activity, education level, among other variables. These factors can further complicate the interaction within the health-disease interplay and associations in this context and may emphasize the need for a multifaceted approach to better understanding and addressing these links.

Study limitations

The study's used conveniently sourced sample from university clinics and it may introduce selection bias and limit generalizability. Additionally, the modified ASA classification system questionnaire may not capture all relevant medical conditions or accurately assess the severity of systemic diseases. The study focused on the associations between HRV and health parameters; however, potential confounding factors were not comprehensively accounted for or controlled in the analysis. Further research is needed to elucidate the underlying mechanisms and determine the clinical significance of these findings.

CONCLUSION

In conclusion, this study underscores the potential of smartphone-derived heart rate variability (HRV) as a complementary diagnostic tool for evaluating both general and oral health conditions. The findings reveal discernible associations between HRV and the American Society of Anesthesiologists (ASA) classification for risk in dentistry, as well as various oral health parameters including tooth loss, oral rehabilitation status, and periodontal disease. Moreover, the study demonstrates the reliability of heart rate measurements derived from smartphones, which were comparable to those obtained through traditional cardiac monitoring devices and, finding comparable signal acquisition between the methods, may suggest a reasonable assessment of heart rate variability (HRV). By integrating HRV monitoring into routine dental care, practitioners may gain additional perspectives and implications into patient health status, stress response, and risk evaluation for dental treatment, ultimately enhancing patient safety. Further research is needed to fully explore the potential of smartphone-derived HRV in dental settings and its implications for overall health assessment.

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AUTHOR'S CONTRIBUTION

LFMG: conceptualization, data curation, investigation, methodology, writing – original draft, writing – review & editing. VCS: data curation, investigation, writing – review & editing. VLP: data curation, investigation, writing – review & editing. ML: data curation, investigation, writing – review & editing. FAS: Conceptualization, methodology, formal analysis, writing – original draft, writing – review & editing. MCB: conceptualization, data curation, investigation, methodology, formal analysis, writing – original draft, writing – review & editing.

CONFLICT OF INTEREST STATEMENT

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Competing interests: The authors declare no conflict of interest and disclose any commercial associations, current and within the past five years, that might pose a potential, perceived or real conflict of interest.

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