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Oral Salivary Predictive Values as a Potential Contributor to Overall Autonomic Balance, Cardiac Coherence, Heartrate Variability, and Cardiovascular Risk Assessment

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SUMMARY

Introduction*:** *As salivary pH and electrolytes are indicators of cardiac health or sympathetic nervous system. This study aims to investigate the relationship between stress, coherence, and autonomic function by analyzing salivary pH and electrolytes as biomarkers of cardiac health and sympathetic nervous system activity.* ***Materials and Methods: *Heartrate Variability (HRV) recordings were taken for six minutes. Saliva samples were collected by the spit method. The specimens were meticulously transferred to the spectroscopy laboratory at a temperature of -20 °C in a dry ice container. Following 30 minutes of centrifugation at 7000 rpm, a transparent supernatant was obtained. Biochemical analysis of saliva samples was performed without further storage and freezing through Fourier transform infrared (FTIR) Spectroscopy.* ***Results*:** *In the male participants with age group 18-29 years containing normal salivary pH, 69.1% had parasympathetic predominance. In the males with age group 18-29 years containing normal, acidic and alkaline salivary pH had low coherence in 67.3%, 88.9% and 66.7% of subjects respectively. Younger age group containing acidic salivary pH, 50% had sympathetic predominance. However, as age increased, the percentage of sympathetic predominance in acidic salivary group increased. i.e. in the 54-65 years age group, 100% had sympathetic predominance. The subjects who had sodium in their saliva were having sympathetic predominance i.e. in the age group of 42-53 years of females who had sodium in their saliva, 100% subjects were having sympathetic predominance.* ***Conclusion*:** *Our study strongly suggests a potential link between oral salivary indicators and autonomic nervous system regulation, which plays a crucial role in cardiovascular health. Oral salivary parameters could serve as potential predictors or indicators of autonomic sympathetic predominance, internal stress, cardiac coherence, and heart rate variability.*

Key words: Saliva, Fourier transform infrared spectroscopy FT-IR, Heart rate variability, Coherence.

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Introduction

Saliva is a complex fluid with multiple functions, ranging from facilitating digestion to protecting oral health. It plays a crucial role in maintaining oral health and has various functions in the digestive and immune systems.[1] Saliva can be influenced by the autonomic nervous system (ANS), which is a branch of the peripheral nervous system responsible for regulating involuntary physiological functions. The ANS has two main divisions: the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS).[2]

The parasympathetic nervous system, increases the production of watery, enzyme-rich saliva, aiding in

digestion. While the sympathetic nervous system, its stimulation tends to result in a decrease in saliva flow and changes in the composition of saliva, and this interaction is often studied in the context of stress response.[3]

Sympathetic predominance indicates stress that can affect both saliva composition and cardiovascular health.[4] Stress-induced changes in saliva, including alterations in pH which is an important factor in maintaining oral health and it may reflect the body's physiological response to stress.[5] Saliva electrolytes, such as sodium, phosphate, chloride, and bicarbonate, proteins can be influenced by (Sympathetic nervous system) SNS activity, which is also closely linked to cardiovascular function and stress responses. In this sense, salivary electrolytes might act as indirect markers of autonomic imbalance or cardiovascular stress.[6]

Heart rate variability, a measure of the variation in time between heartbeats, is often used as an indicator of autonomic nervous system balance.[7] Changes in HRV have been associated with alterations in salivary flow and composition, providing insights into the complex interplay between the sympathetic and parasympathetic branches of the autonomic nervous system.[8]

Heart rate variability, which reflects the autonomic regulation of the heart, has been studied in relation to saliva where they have mentioned that subjects with sympathetic predominance had higher level of cortisol in the saliva. Understanding the interplay between the autonomic nervous system and saliva has implications for research on stress, mental health, and various medical conditions.[9]

Cardiac Coherence is a state of cooperative alignment between the heart, mind, emotions and physical systems. It's important that while there is a connection between saliva and the autonomic nervous system and cardiac health, the interpretation of salivary pH and electrolytes considering various factors that can influence saliva composition.[10] The objectives of this study were to examine the utility of salivary pH and electrolytes as indicators of physiological stress responses, autonomic function, and cardiac health, and to explore their potential as non-invasive biomarkers for assessing coherence and overall cardiovascular well-being.

Methodology

This cross-sectional study was conducted in the dental section of tertiary care hospital. Sample size of 323 subjects (using Open EPI software version 2.01) using the findings of Suresh et al.[11] This study included healthy individuals without previous medical history of any disease or psychological disorder, individuals with multiple occupations, age more than 18 years, and who signed a consent form. The study excluded individuals who were unwilling to participate or have any past medical history of disease or taking medicine of any kind. All the study participants were explained about the study one day prior to their report in their study room, and those who gave their consent were requested to report next day at 10:00 am in the morning. The subjects were kept in a quiet calm and temperature regulated room and were given 30 minutes to relax. After this HRV (HeartMath, LLC 14700 West park ave boulder creek, CA) recordings were taken for six minutes by applying HRV sensors either on index finger or ear lobe in relax sitting position according to the choice of study subjects. HRV uses baevsky stress index to evaluate stress levels. The Baevsky Stress Index (BSTRi), calculated from Heart Rate Variability (HRV) data, has been proposed for quantitative assessment of physiological stress, with higher scores indicating higher levels of physical and/or psychological stress.[12] Subsequently, HRV data was analysed using emWave pro plus software which is an advanced tool for analysing and preparing the data from HRV from which parasympathetic or sympathetic predominance and coherence was measured (Figure 1). Furthermore, Kubios method analysis software of HRV was also used for HRV data analysis, which is a cutting-edge and simple to use freeware for coronary HRV analysis.[13] It comprises an improvised QRS detection algorithm and tools for noise correction, trend removal and analysis sample selection.

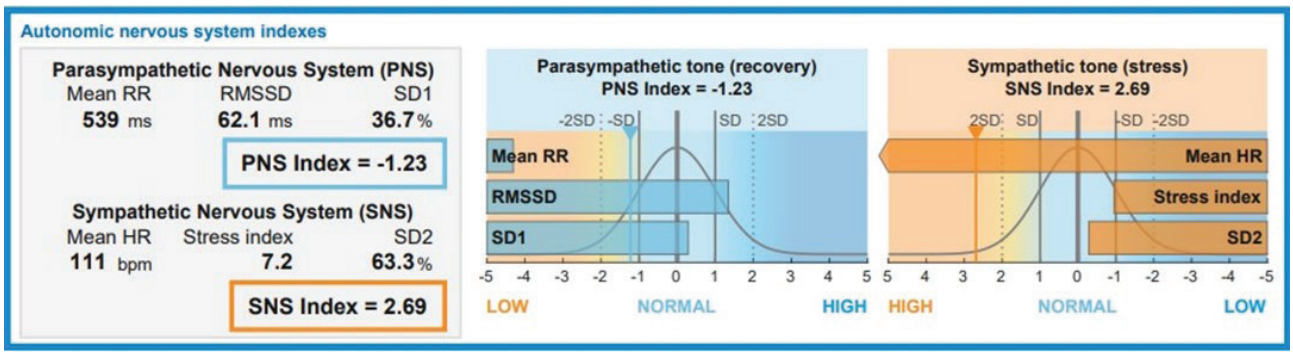

Figure 1: Autonomic Nervous System Indices.

For Saliva collection the samples were collected by the spit method. It was prohibited to eat or drink for at least 1 hour before collection of saliva. Saliva collection occurred in the morning between 9 and 12 AM. Prior to the collection of saliva, subjects were asked to rinse their mouth with water and then wait for 1-2 min for water clearance. Unstimulated whole saliva was then collected by making the subjects sit in the upright position with head slightly inclined.[14] 2ml of unstimulated saliva was collected in a sterile Eppendorf tube and immediately were stored in a freezer (−80 °C). Samples were transported into dry ice container (−20 °C) to the spectroscopy laboratory,[15] of tertiary care hospital. Saliva samples were centrifuged at 7000 rpm for 30 minutes and the clear supernatant was obtained. After centrifuge the IR spectra, (which is Infrared spectroscopy is the measurement of the interaction of infrared radiation with matter by absorption, emission, or reflection) of saliva samples were obtained, and biochemical analysis (i.e. Water, sodium, proteins, calcium, phosphate and chloride) was performed without further storage and freezing through Fourier transform infrared (FTIR) Spectroscopy. FTIR basically works on the principle of absorption of an infrared light source on the sample. An intense wavelength of infrared light is passed through the sample. The FTIR instrument measures the absorption wavelengths. [16]

For Saliva pH one drop of saliva was measured using a pH strip which has a reading from 0 to 14 (acidic pH < 7 and alkaline pH > 7 and neutral = 7). [17] pH was assessed in accordance with the colour change on the indicator paper strips, which gets either lighter or darker in colour when it comes in contact with saliva. Subsequent increase in lightness of shade suggests increase in acidity and increase in darkness suggests increase in basicity. [18]

Statistical analysis

Statistical analysis was performed using SPSS version 23. The frequency and percentages were reported for categorical variables such as gender and occupation.

Results

In the male participants with age group 18-29 years containing normal salivary pH, 69.1% had parasympathetic predominance. In subjects with acidic pH in the same age group, 55.6% were having sympathetic predominance. However, 66.7% had parasympathetic predominance in subjects with Alkaline pH. Furthermore, in subjects with normal and acidic salivary pH, the percentages of sympathetic predominance increased with age.

In the males with age group 18-29 years containing normal, acidic and alkaline salivary pH had low coherence in 67.3%, 88.9% and 66.7% of subjects respectively. In the females with age group 18-29 years containing acidic salivary pH, 50% had sympathetic predominance. However, as age increased, the percentage of sympathetic predominance in acidic salivary group increased. i.e. in the 54-65 years age group, 100% had sympathetic predominance.(Table 1)

Table 1: Percentages of normal acidic and alkaline salivary pH according to ANS, Coherence and stress index

Gender	Age group	Saliva PH	ANS dominance		Coherence				Stress Index		
			Parasympathetic	Sympathetic	Basic	Good	Very good	Excellent	Low	Moderate	Higher
Male N = 161	**18-29 years** N = 67	Normal	69.1	30.9	67.3	29.1	1.8	1.8	72.7	12.7	14.5
		Acidic	44.4	55.6	88.9	11.1	0	0	44.4	22.2	33.3
		Alkaline	66.7	33.3	66.7	33.3	0	0	66.7	33.3	0
	30-41 years N = 43	Normal	45.2	54.8	67.7	32.3	0	0	51.6	16.1	32.3
		Acidic	44.4	55.6	66.7	33.3	0	0	44.4	11.1	44.4
		Alkaline	33.3	66.7	100	0	0	0	33.3	33.3	33.3
	42-53 years N = 27	Normal	33.3	66.7	94.4	5.6	0	0	38.9	44.4	16.7
		Acidic	50	50	83.3	16.7	0	0	33.3	33.3	33.3
		Alkaline	66.7	33.3	66.7	33.3	0	0	66.7	33.3	0
	54-65 years N = 24	Normal	30.8	69.2	76.9	23.1	0	0	30.8	15.4	53.8
		Acidic	28.6	71.4	85.7	14.3	0	0	57.1	14.3	28.6
		Alkaline	25	75	75	25	0	0	25	25	50
Female N = 162	**18-29 years** N = 70	Normal	43.3	56.7	75	23.3	1.7	0	50	23.3	26.7
		Acidic	50	50	62.5	25	12.5	0	62.5	12.5	25
		Alkaline	50	50	50	50	0	0	50	0	50
	30-41 years N = 58	Normal	40	60	62.2	35.6	2.2	0	48.9	22.2	28.9
		Acidic	33.3	66.7	77.8	11.1	11.1	0	33.3	22.2	44.4
		Alkaline	75	25	50	50	0	0	75	25	0
	42-53 years N = 24	Normal	42.9	57.1	85.7	14.3	0	0	42.9	14.3	42.9
		Acidic	33.3	66.7	88.9	11.1	0	0	33.3	11.1	55.6
		Alkaline	100	0	100	0	0	0	100	0	0
	54-65 years N = 10	Normal	25	75	75	25	0	0	37.5	25	37.5
		Acidic	0	100	100	0	0	0	0	50	50
		Alkaline	-	-	-	-	-	-	-	-	-

Table 2: Percentages of presence of salivary components in male subjects according to ANS, Coherence and stress index

Gender	Age group	FTIR	ANS dominance		Coherence				Stress index		
			Parasympathetic	Sympathetic	Basic	Good	Very good	Excellent	Low	Moderate	Higher
Male N = 161	18-29 years N = 67	Water	100	100	100	100	100	100	100	100	100
		Sodium	70.5	73.9	76.6	58.8	50	100	69.6	66.7	83.3
		Proteins	79.5	73.9	72.3	100	0	100	80.4	66.7	75.0
		Calcium	47.7	43.5	48.9	47.1	0	0	52.2	33.3	33.3
		Phosphate	61.4	82.6	70.2	58.8	100	100	60.9	88.9	83.3
		Chloride	9.1	17.4	17	0	0	0	8.7	11.1	25.0
	30-41 years N = 43	Water	100	100	100	100	-	-	100	100	100
		Sodium	73.7	79.2	83.3	61.5	-	-	71.4	85.7	80
		Proteins	78.9	70.8	76.7	69.2	-	-	81.0	57.1	73.3
		Calcium	26.3	25	16.7	46.2	-	-	23.8	14.3	33.3
		Phosphate	63.2	70.8	60	84.6	-	-	57.1	71.4	80
		Chloride	10.5	4.2	6.7	7.7	-	-	9.5	0	6.7
	42-53 years N = 27	Water	100	100	100	100	-	100	100	100	100
		Sodium	81.8	93.8	91.7	50	-	100	81.8	90	100
		Proteins	54.5	62.5	62.5	50	-	0	63.6	50	66.7
		Calcium	9.1	50	37.5	0	-	0	18.2	40	50
		Phosphate	36.4	87.5	70.8	50	-	0	36.4	90	83.3
		Chloride	18.2	6.3	8.3	50	-	0	18.2	0	16.7
	54-65 years N = 24	Water	100	100	100	100	-	-	100	100	100
		Sodium	42.9	94.1	84.2	60	-	-	55.6	100	90.9
		Proteins	42.9	35.3	36.8	40	-	-	33.3	25	45.5
		Calcium	42.9	17.6	31.6	0	-	-	33.3	0	27.3
		Phosphate	71.4	88.2	78.9	100	-	-	77.8	100	81.8
		Chloride	100	11.8	10.5	0	-	-	0	0	18.2

Table 3: Percentages of presence of salivary components in female subjects according to ANS, Coherence and stress index

Gender	Age group	FTIR	ANS dominance		Coherence				Stress index		
			Parasympathetic	Sympathetic	Basic	Good	Very good	Excellent	Low	Moderate	Higher
Female N = 162	18-29 years N = 70	Water	100	100	100	100	100	-	100	100	100
		Sodium	67.7	82.1	78.4	64.7	100	-	63.9	86.7	89.5
		Proteins	74.2	69.2	72.5	64.7	100	-	72.2	53.3	84.2
		Calcium	32.3	23.1	27.5	23.5	50	-	27.8	26.7	26.3
		Phosphate	61.3	76.9	72.5	70.6	0	-	63.9	73.3	78.9
		Chloride	9.7	10.3	3.9	29.4	0	-	11.1	0	15.8
	30-41 years N = 58	Water	100	100	100	100	100	-	100	100	100
		Sodium	70.8	88.2	78.4	84.2	100	-	75	92.3	82.4
		Proteins	83.3	61.8	62.2	84.2	100	-	78.6	69.2	58.8
		Calcium	45.8	26.5	27	47.4	50	-	39.3	38.5	23.5
		Phosphate	62.5	82.4	70.3	84.2	50	-	67.9	76.9	82.5
		Chloride	0	5.9	5.4	0	0	-	0	0	11.8
	42-53 years N = 24	Water	100	100	100	100	-	-	100	100	100
		Sodium	60	100	85.7	66.7	-	-	60	100	100
		Proteins	60	71.4	66.7	66.7	-	-	60	66.7	72.7
		Calcium	20	28.6	23.8	33.3	-	-	20	66.7	18.2
		Phosphate	30	85.7	71.4	0	-	-	30	100	81.8
		Chloride	10	7.1	4.8	33.3	-	-	10	0	9.1
	54-65 years N = 10	Water	100	100	100	100	-	-	100	100	100
		Sodium	100	87.5	87.5	100	-	-	100	66.7	100
		Proteins	100	75	75	100	-	-	100	66.7	75
		Calcium	100	50	50	100	-	-	100	66.7	25
		Phosphate	0	100	100	0	-	-	33.3	100	100
		Chloride	50	12.5	12.5	50	-	-	33.3	0	25

FTIR data of the study showed that the subjects who had sodium in their saliva were having sympathetic predominance i.e. in the age group of 42-53 years of females who had sodium in their saliva, 100% subjects were having sympathetic predominance. However, the calcium in saliva was present in subjects who had parasympathetic predominance. Similarly, subjects with low coherence had the frequent presence of sodium in their saliva. Furthermore, there were mixed low and good percentages of subjects with presence of calcium in their saliva. Regarding the stress index, subjects who had sodium in their saliva also had higher stress index score.

In the age group of 18-29 years males with sodium in their saliva, 83.3% had higher stress index score. Furthermore, the presence of calcium in the saliva were having low stress index score. In the age group of 18-29 years females with calcium in the saliva, 27.8% had low stress index scores. Furthermore, the subjects who had phosphate in their saliva were having sympathetic predominance i.e. in the age group of 18-29 years of males who had phosphate in their saliva, 82.6% subjects were having sympathetic predominance. Likewise, subjects with low coherence had the presence of phosphate in the saliva. Phosphate was also present in the saliva of subjects with higher stress index.

Subjects with proteins in the saliva had low coherence and low stress index. In the age group of 18-29 years males with proteins in the saliva, 100 % had excellent coherence and 80.4% had low stress index. It was also noted that subjects with higher stress index had presence of chloride in the saliva. (Table 2 and 3).

Discussion

The regulation of salivary secretion involves a reflex arc, which includes receptors and nerves that respond to the actions of tasting and chewing, a salivation center, and autonomic nerves that control salivation.[19] Accordingly, the sympathetic and parasympathetic systems control salivation, composition, and its function.[20] A recent study shows that the two systems work together to produce saliva, which contains both fluid and protein components.[21] As the regulation of salivary pH is influenced by the sympathetic and parasympathetic nervous system. Thus, it can be considered as a biomarker of stress.[22]

However, in a study of Masa Ieda. Et al there were no significant differences between study groups (schizophrenia compared with controls) in sympathetic nervous system (SNS) activity with relation to salivary pH.[23] The result of our study shows that subjects with normal and acidic salivary pH, the percentages of sympathetic predominance increased with age. According to another study there are multiple factors and complex oral environment that may affect the salivary pH and autonomic nervous system activity.[24] Whereas in our study there were mixed autonomic nervous system predominance found in subjects with normal or alkaline pH.

One study, based on a population of 183 subjects, investigated associations between sense of coherence and stress levels with saliva and found that there was Inverse significant associations between sense of coherence, but no significant association seen in stress levels.[23]

However this study results indicates that there is a significant low coherence state and higher stress levels seen in both male and female participants with acidic salivary pH. Stress can alter the pH balance of saliva, making it more acidic.[25] As a result increased acidity may contribute to dental issues, affecting oral health and potentially causing discomfort that could impact on coherence and alteration in autonomic nervous system activity. [26]

Cardiovascular diseases are a leading cause of death all over the world. Enzymes, proteins and electrolytes found in saliva, have been used for post-operative control of patients who had cardiovascular surgery.[27] A study found the direct relationship between raised levels of salivary enzymes and electrolytes and heart rate which increases under stress.[28]

Sodium plays a role in the regulation of blood pressure. And is one of the electrolytes that helps maintain the balance of fluids in and around cells. Electrolyte imbalances can have systemic effects, impacting various physiological processes, including those related to the cardiovascular system. [30]

Labat C et al. where they collected saliva from hypertension and non-hypertension group, found that all salivary electrolytes, except sodium, were significantly associated with age and no significant associations between sodium and heart rate were observed.[31] While this study found that the subjects who had sodium and phosphate in their saliva were having sympathetic predominance with increasing age in both male and female groups.

Hypertension is a common cardiovascular disease risk factor. Hypertension can be caused by excessive sodium intake, hence monitoring sodium levels in bodily fluids, including saliva, may provide some insights into dietary habits.[32] As our study found that subjects with low coherence and higher stress index had the frequent presence of sodium, phosphate and chloride in their saliva.

There is a connection between calcium metabolism in the body and cardiovascular health. Calcium is vital for the contraction of cardiac muscles, during each heartbeat, calcium ions are involved in the contraction and relaxation of the heart muscle (myocardium). Proper calcium regulation is necessary for maintaining a regular heart rhythm and optimal cardiac function.[33] This study found that calcium in saliva was present in subjects who had parasympathetic predominance. Those subjects had low

stress index score and good coherence. Whereas a study by Singh V et al, believed that calcium play an important role in protection against dental decay.[34] Furthermore a recent study found a significant correlation between salivary calcium levels and salivary pH in hypertensive females. And also salivary calcium levels with a significant correlation with systolic blood pressure.[35]

There is emerging evidence suggesting that certain saliva proteins may be linked to cardiovascular health. In a proteomic research of salivary biomarkers, Rao et al. identified 487 unique proteins of which 33% of these had not been previously reported in human saliva. Sixty-five proteins were markedly expressed between samples predominantly involved in regulating metabolism and immune response pathways.[36] Sun et al. proved that many salivary glycoproteins were associated with age, gender, and immunity.[37] In this study participants with proteins in the saliva, had highest of 100% excellent coherence and had low stress index.

Since approximately 27% of the whole saliva proteins resemble those found in plasma, similar proteins present in both saliva and plasma will be very useful to facilitate monitoring of cardiac disease progression and revealed as significant biomarkers. [38]

Conclusion

Younger age groups with parasympathetic predominance had normal salivary pH and with sympathetic predominance had acidic salivary pH. As the age increased, sympathetic predominance also increased leading to acidic salivary pH. Furthermore, subjects who had low coherence and high stress index had increased frequency of acidic saliva. Regarding the salivary electrolytes, increased frequency of sodium presence was shown in subjects with sympathetic predominance and high stress index. Subjects with proteins in the saliva had low coherence and low stress index.

Cardiovascular diseases are multifactorial, and changes in pH and electrolyte levels is one of the aspects of a complex interplay of factors. Hence, relationship between saliva pH and electrolyte levels, such as sodium, phosphate, chloride, calcium, salivary proteins and their potential use for the early diagnosis of cardiac health is very important.

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