EFFECT OF CIGARETTE SMOKING AND CESSATION OF SMOKING ON HEART RATE VARIABILITY

BY

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DISSERTATION SUBMITTED TO

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION & RESEARCH,

TAMAKA, KOLAR, KARNATAKA

IN PARTIAL FULFILLMENT

OF THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF MEDICINE
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Under the guidance of

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DEPARTMENT OF PHYSIOLOGY
SRI DEVARAJ URS MEDICAL COLLEGE, KOLAR

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"EFFECT OF CIGARETTE SMOKING AND CESSATION OF SMOKING ON HEART RATE VARIABILITY"

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MEMBER SECRETARY **PRINCIPAL**

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In the end, I thank The Almighty for the blessing for the fulfillment of this work.

Date:

Place: Kolar *Dr. PADMINI THALANJERI*

LIST OF ABBREVIATIONS

HRV	-	Heart Rate Variability
ANS	-	Autonomic Nervous System
SDNN	-	Standard Deviation from Normal to Normal
PNS	-	Parasympathetic Nervous System
SNS	-	Sympathetic Nervous System
HR	-	Heart Rate
NE	-	Norepinephrine
ATP	-	Adenosine Tri Phosphate
SAN	-	Sino Atrial Node
BP	-	Blood Pressure
ECG	-	Electrocardiography
VLF	-	Very Low Frequency
LF	-	Low Frequency
HF	-	High Frequency
SAN	-	Sino Atrial Node
REM	-	Rapid Eye Movement
CHD	-	Coronary Heart Disease
RSA	-	Respiratory Sinus Arrhythmia

ABSTRACT

Background and objectives:

Long term cigarette smoking is an independent risk factor for cardiovascular morbidity and mortality. It is a strong risk factor for acute ischemic cardiac events such as myocardial infarction, ventricular arrhythmias and sudden death in which dysfunction of the autonomic nervous system may be an important causal component. Heart Rate Variability provides a powerful means of observing the interplay between sympathetic and parasympathetic nervous system. Smoking not only affects the health of smokers but is also detrimental to passive smokers.

Smoking has been shown to influence the tone of the autonomic nervous system as reflected by heart rate variability (HRV). Reduced heart rate variability has been used as a marker of reduced vagal activity and is a valuable non-invasive tool in assessment of cardiovascular autonomic function. Heart rate variability refers to the beat to beat alteration in heart rate.

It has been shown that cessation of smoking results in increase in heart rate variability which is comparable to that of nonsmokers.

Few studies have been done till date by using time domain measure of HRV in South Indian population to record the effect of smoking and also the changes obtained following cessation of smoking for a duration of 1 week. With this background the present study of effect of cigarette smoking and its cessation on heart rate variability has been carried out.

Materials & Methods:

Thirty five smokers and thirty five age matched controls who were non smokers were selected considering the inclusion and exclusion criteria. Information was collected regarding their smoking history and was subjected to HRV analysis using BPL CARDIART 8408 VIEW machine. The resulting data was statistically analysed.

Results:

HRV recorded were significantly reduced in study group (smokers) than controls. Further, HRV recorded among the study group after they quit smoking for one week was significantly higher than during smoking period. The increase in HRV among the study group following cessation of smoking was comparable to that of non smokers. There was a negative correlation between pack years of smoking and the HRV among smokers which was not significant.

Conclusion:

There is reduction in HRV indicating sympathetic predominance among cigarette smokers. Furthermore, there is an immediate and substantial increase in HRV after cessation of smoking for one week. The increase in HRV was comparable to that of non smokers. The clinical implications seem to be quite favourable even for individuals who have been long-term cigarette smokers.

Key words: Cigarette smoking, heart rate variability, autonomic nervous system.

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INTRODUCTION

INTRODUCTION

The last two decades have witnessed the recognition of a significant relationship between the autonomic nervous system and cardiovascular mortality, including sudden cardiac death. Various risk factors like age, sedentary lifestyle, food habits, deranged lipid profile have been known to play a role in the development of cardiovascular morbidity and mortality of which cigarette smoking also plays a major role.

Long term cigarette smoking is an independent risk factor for cardiovascular morbidity and mortality. It is a strong risk factor for acute ischemic cardiac events such as myocardial infarction, ventricular arrhythmias and sudden death in which dysfunction of the autonomic nervous system may be an important causal component. Smoking not only affects the health of smokers but is also detrimental to passive smokers. Smoking has been shown to influence the tone of the autonomic nervous system as reflected by heart rate variability (HRV).

Heart Rate Variability (HRV) represents one of the most promising markers for detecting sympatho-vagal imbalance. HRV has become the conventionally accepted term to describe variations of both instantaneous heart rate and RR intervals. To describe oscillation in consecutive cardiac cycles, other terms have been used in the literature, for example, cycle length variability, heart period variability, RR variability and RR interval tachogram and they more appropriately emphasize the fact that it is the interval between consecutive beats that is being analyzed rather than heart rate per se. Heart Rate Variability provides a powerful means of observing the interplay between sympathetic and parasympathetic nervous system.

Reduced heart rate variability has been used as an indicator of reduced vagal

activity and is a valuable non-invasive tool in assessment of cardiovascular autonomic function. It has been shown that cessation of smoking results in increase in heart rate variability which is comparable to that of nonsmokers.

Few studies have been done till date by using time domain measure (SDNN) to record HRV in smokers and also the effect of cessation of smoking on HRV on those volunteers who quit subsequently for a duration of 1 week. Hence the present study has been carried out to study the effect of smoking and the effect of quitting smoking on heart rate variability.

AIMS AND OBJECTIVES

AIMS AND OBJECTIVES OF THE STUDY

1. To compare the HRV of smokers and non smokers.

2. To compare the HRV of smokers and their HRV after quitting smoking for 1 week.

3. To compare HRV of non smokers at the beginning and after one week.

4. To compare HRV of smokers after they quit smoking with that of non smokers.

5. To correlate HRV of smokers with pack years of smoking.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

A. HEART RATE AND REGULATION OF HEART RATE:

Heart rate is normally determined by the pacemaker activity of the sinoatrial node (SA node) located in the posterior wall of the right atrium. The SA node exhibits automaticity. This intrinsic automaticity, if left unmodified by neurohumoral factors, exhibits a spontaneous firing rate of 100-115 beats/min.

Heart rate is decreased below the intrinsic rate primarily by activation of the vagus nerve innervating the SA node. Normally, at rest, there is significant vagal tone on the SA node so that the resting heart rate is between 60 and 90 beats/min. For heart rate to increase above the intrinsic rate, there is both a withdrawal of vagal tone and an activation of sympathetic nerves innervating the SA node.

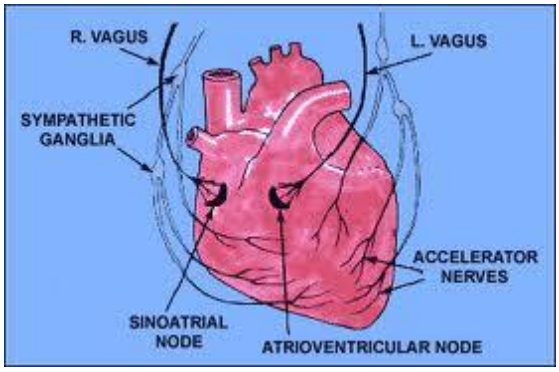
Heart rate is also modified by circulating catecholamines acting via β_1-adrenoceptors located on SA nodal cells.

INNERVATION OF THE HEART:

The SAN is under the control of the parasympathetic (vagal, PNS) and sympathetic nervous system (SNS). Both left and right vagus nerves stimulate the SAN (the right nerve is dominant and reduces HR), the AV node (left nerve is dominant and prolongs AV conduction) as well as the atrium muscle, whereas efferent control of the ventricle muscle is still unclear. In general, activity within the vagal nerves decreases HR when the stimulatory effect of the right nerve dominates. Postganglionic sympathetic fibres innervate almost all centres of the heart including the AV, heterotrophic centres, atrium

and ventricle myocardium. Activity within the right Ansa subclavia (right sympathetic nerve) mostly influences HR, whereas left Ansa subclavia activity impacts stroke volume. Under resting conditions, both branches of the ANS are tonically active when regulating cardiac activity with a dominance of vagal regulation. Rapid changes in HR are always caused by shifts in vagal regulation.

1. Innervation of heart



B. AUTONOMIC NERVOUS SYSTEM

The autonomic nervous system is the part of the peripheral nervous system that acts as a control system functioning largely below the level of consciousness and controls visceral functions. The ANS affects heart rate, digestion, respiratory rate, salivation, perspiration, diameter of the pupils, micturition and sexual arousal.

Whereas most of its actions are involuntary, some, such as breathing, work in tandem with the conscious mind. It is classically divided into two subsystems: the parasympathetic nervous system (PNS) and sympathetic nervous system (SNS).

With regard to function, the ANS is usually divided into sensory (afferent) and motor (efferent) subsystems. Within these systems, however, there are inhibitory and excitatory synapses between neurons.

SYMPATHETIC DIVISION:

The sympathetic division has thoracolumbar "outflow", meaning that the neurons begin at the thoracic and lumbar (T1-L2) portions of the spinal cord. The sympathetic division (thoracolumbar outflow) consists of cell bodies in the lateral horn of spinal cord (intermediolateral cell columns) from T1 to L2.

There are several locations upon which preganglionic neurons can synapse for their postganglionic neurons:

1. Paravertebral ganglia of the sympathetic chain (these run on either side of the vertebral bodies)

2. Prevertebral ganglia (celiac ganglia, superior mesenteric ganglia, inferior mesenteric ganglia)

3. Chromaffin cells of adrenal medulla (this is the one exception to the two-neuron pathway rule: synapse is direct onto cell bodies)

These ganglia provide the postganglionic neurons from which innervation of target organs follows. Examples of splanchnic (visceral) nerves are:

1. Cervical cardiac nerves & thoracic visceral nerves which synapse in the sympathetic chain

2. Thoracic splanchnic nerves (greater, lesser, least) which synapse in the prevertebral ganglion

3. Lumbar splanchnic nerves which synapse in the prevertebral ganglion

4. Sacral splanchnic nerves which synapse in the inferior hypogastric plexus

PARASYMPATHETIC DIVISION:

The parasympathetic division has craniosacral outflow, meaning that the neurons begin at the cranial nerves (CN III, CNVII, CN IX, CNX) and sacral (S2-S4) spinal cord. The parasympathetic division (craniosacral outflow) consists of cell bodies from one of two locations: brainstem (Cranial Nerves III, VII, IX, X) or sacral spinal cord (S2, S3, S4).

These are the preganglionic neurons, which synapse with postganglionic neurons in these locations:

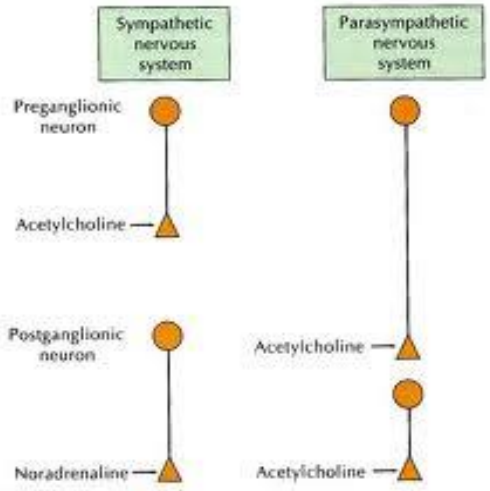
1. Parasympathetic ganglia of the head- Ciliary (CN III), Submandibular (CN VII), Pterygopalatine (CN VII), Otic (CN IX)
2. In or near wall of organ innervated by Vagus (CN X), Sacral nerves (S2, S3, S4))

These ganglia provide the postganglionic neurons from which innervations of target organs follows. Examples are:

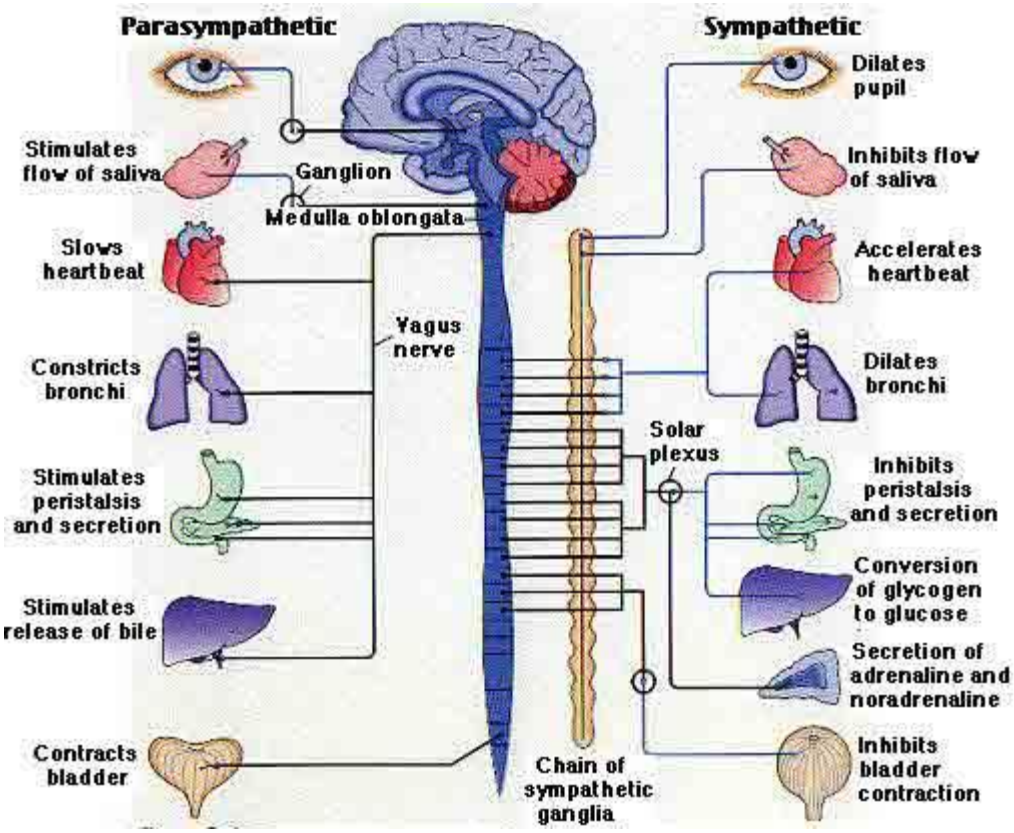
1. The preganglionic parasympathetic splanchnic (visceral) nerves
2. Vagus nerve, which wanders through the thorax and abdominal regions innervating, among other organs, the heart, lungs, liver and stomach.

The ANS is unique in that it requires a sequential two-neuron efferent pathway; the preganglionic neuron must first synapse onto a postganglionic neuron before innervating the target organ. The preganglionic neuron will begin at the “outflow” and will synapse at the postganglionic neuron’s cell body. The post ganglionic neuron will then synapse at the target organ.

2. Organization of ANS:



3. Functional distribution of ANS:



C. CARDIOVASCULAR AUTONOMIC REGULATION:

Fluctuations in heart rate (HR) and blood pressure (BP) reflect the dynamic response of the cardiovascular control system to physiological changes. The HR is controlled by membrane processes of the sinoatrial node, which is modulated by innervations from both the parasympathetic and sympathetic divisions of the ANS. The heart receives extrinsic efferent (sympathetic and parasympathetic) and afferent innervations, and possesses intracardiac nerve supplies. This intracardiac intrinsic nervous system interacts with efferent nerve fibres in a complex manner to help maintain adequate cardiac output. Noradrenaline and acetylcholine are the predominant neurotransmitters utilized by the heart, although many other types of neurotransmitters or neuromodulators have been localised in cardiac nerves.

The main periodic fluctuations are respiratory sinus arrhythmia (RSA), baroreflex related and thermoregulation related variability of the HR. Perhaps the most conspicuous fluctuation is the effect of respiration on HR which is the RSA, seen as oscillations in the R-R intervals in the frequency range of 0.15-0.4 Hz, which are generally believed to be mediated predominantly by fluctuations of vagal-cardiac nerve traffic and thus reflect vagal activity. The HR accelerates during inspiration and decelerates during expiration, and the magnitude of this response depends on the rate and the depth of the respiration. Although RSA can be abolished by atropine or vagotomy, it has been shown to be a somewhat imperfect index of vagal activity and the sympatho-vagal balance in HRV analysis.

Furthermore, it has been shown that arterial BP variations significantly influence the amplitude of HR variations in the deep breathing test. Slower fluctuations in the HR

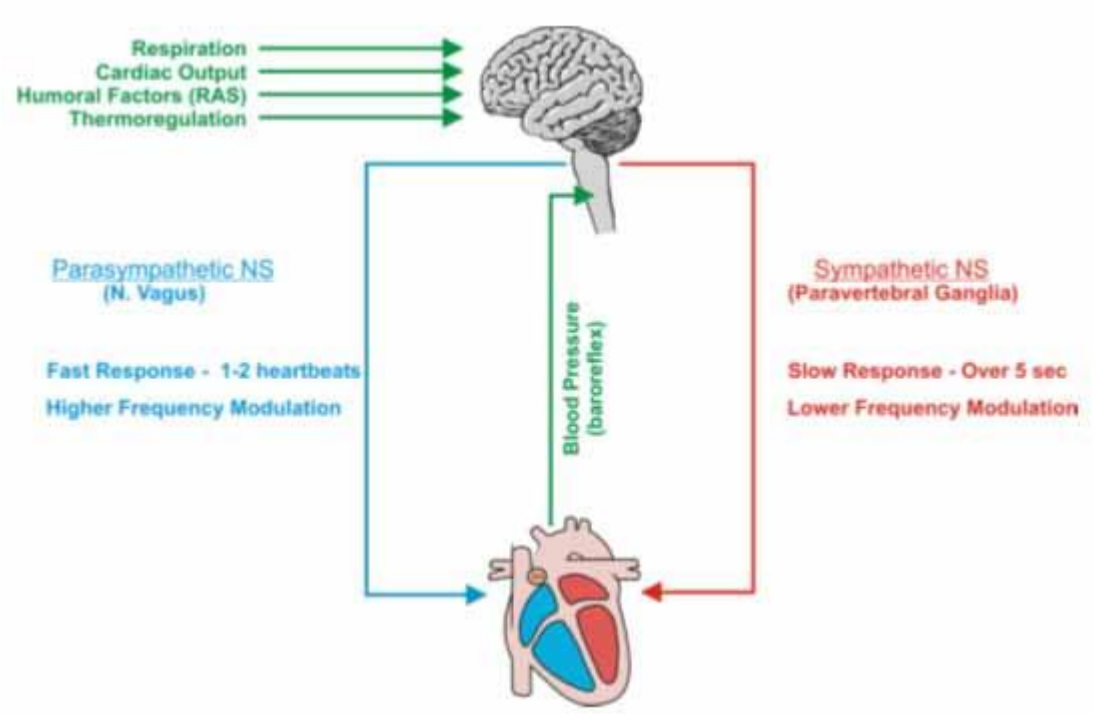
than in the RSA occur at around 0.1 Hz, and this fluctuation in the HR originates from self-oscillation in the vasomotor part of the baroreflex loop as a result of negative feedback in the baroreflex and is accompanied by synchronous fluctuations in the blood pressure known as Meyer waves. This fluctuation decreases with both parasympathetic and sympathetic blockade. Yet slower fluctuations are thought to arise from thermoregulatory peripheral blood flow adjustments and are mediated by the sympathetic nervous system. The neural regulation of the circulatory function operates mainly through the interplay of the sympathetic and vagal outflows. In most physiological conditions, the activation of either one of these outflows is accompanied by the inhibition of the other.

The sympathovagal balance is tonically and phasically modulated by the interaction of at least three major factors: central neural integration, peripheral inhibitory reflex mechanisms (with negative feedback characteristics), and peripheral excitatory reflex mechanisms (with positive feedback characteristics). The insular and medial prefrontal cortical areas and the extended amygdala (the central nucleus of the amygdala and the nucleus of the stria terminalis) are involved in high-order processing of autonomic control. Reciprocal interactions between all components of the central autonomic system allow continuous feedback interactions and integration of autonomic responses.

Transmission of information within the central autonomic network involves several neurotransmitters, including amino acids, acetylcholine, monoamines and neuropeptides. Amino acids mediate rapid, point-to-point communication through ion channel receptors. Acetylcholine, monoamines and neuropeptides mediate slower modulatory influences mainly through G-protein (guanosine triphosphate-binding protein) coupled receptors.

The best-known negative feedback mechanism is the baroreceptor reflex. The baroreceptors, which are mainly located in the carotid sinuses, are sensitive to pressure and are referred to as high-pressure receptors. Afferent fibres join the vagus and glossopharyngeal nerves and connect the cardiovascular centers of the medulla oblongata. Increased arterial pressure increases the firing frequency of the afferent impulses to the CNS, causing a tonic suppression of the cardiovascular sympathetic drive and an increase in the parasympathetic vagal drive, which results in a decrease in the HR and in peripheral resistance. An initial decrease in blood pressure has opposite effects.

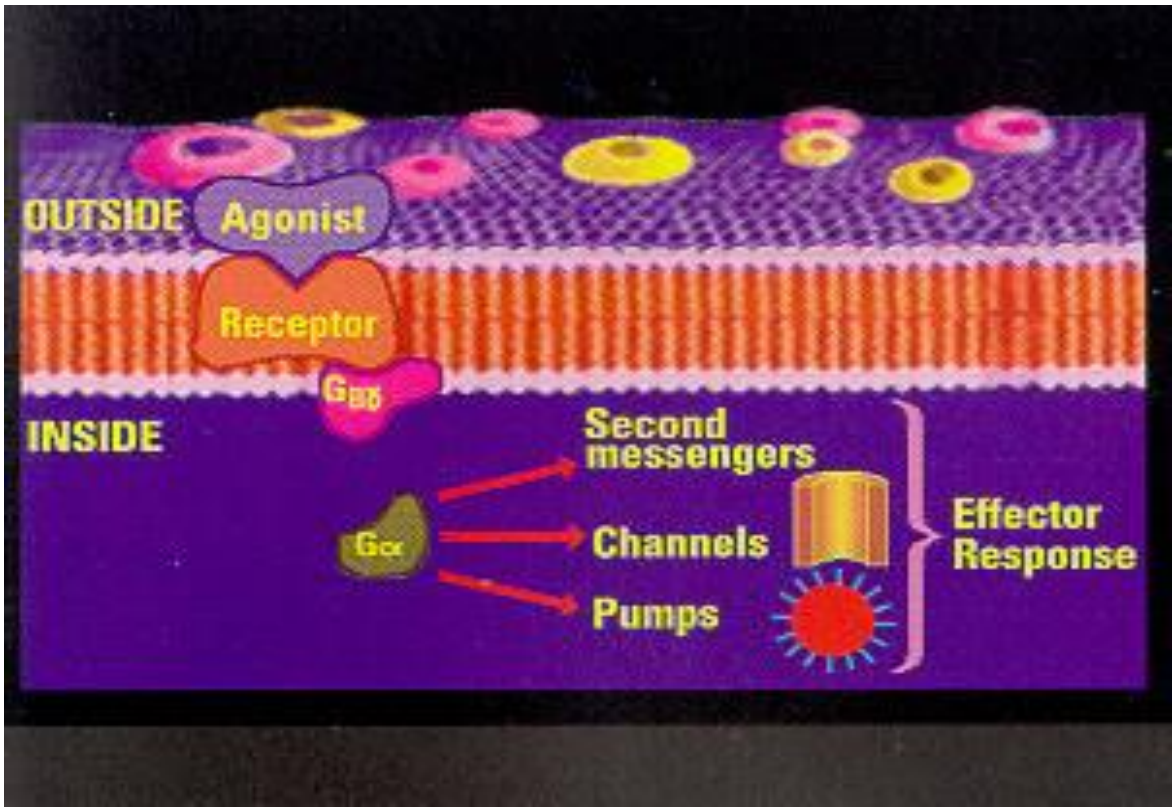
4. Scheme showing the baroreflex functionality:



MECHANISM OF ACTION OF SNS ON SAN.

For most organs including heart, the SNS stimulates organ's functioning. An increase in sympathetic stimulation causes increase in HR, stroke volume, systemic vasoconstriction. The heart response time to sympathetic stimulation is relatively slow. It takes about 5 seconds to increase HR after actual onset of sympathetic stimulation and almost 30 seconds to reach its peak steady level. The delayed HR response occurs due to catecholamine mediated activation of membrane bound enzyme, adenylyl cyclase through a regulatory G protein.

5. Mechanism of action of catecholamine on SA node:



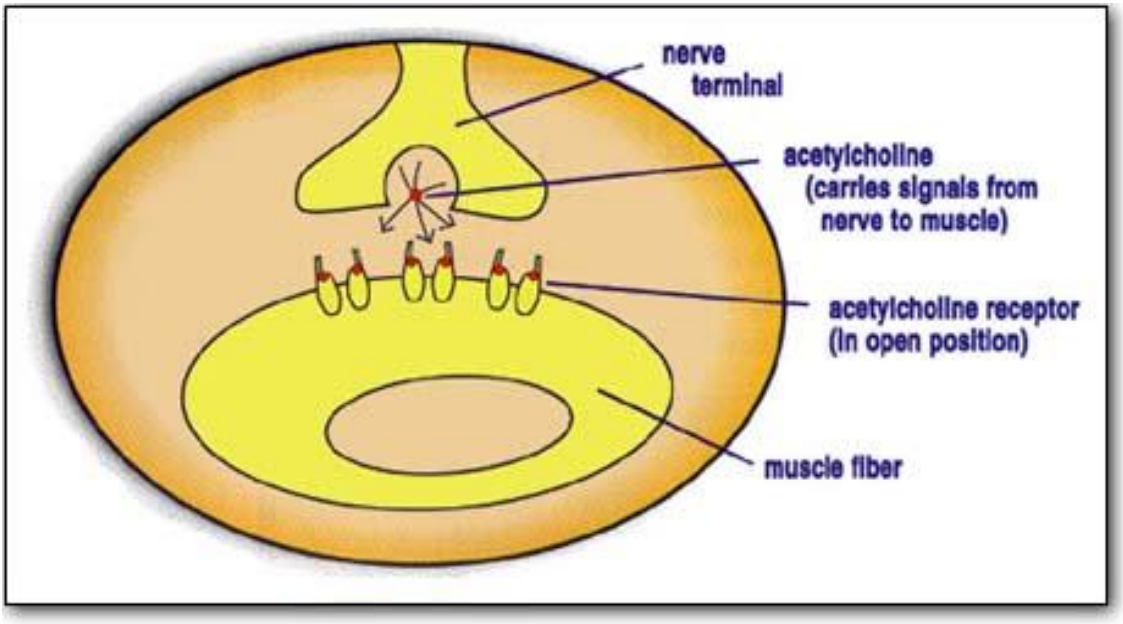
NE binds to the $beta_1$-receptor (Alpha subunit of G-protein). After binding, G protein links to second messenger (adenyl cyclase) which converts ATP to cAMP. cAMP

activates protein kinase A which breaks ATP to ADP + phosphate which phosphorylates the pacemaker channels and increases HR.

MECHANISM OF ACTION OF PNS ON SAN:

In contrast, the PNS inhibits functioning of those organs. An increase in parasympathetic stimulation causes decrease in HR. The heart response time to parasympathetic stimulation is almost instantaneous. During the cardiac cycle, depending on the level of stimulation it takes just 1 or 2 heartbeats before it slows down.

6. Mechanism of action of acetylcholine on SA node:



Acetylcholine neurotransmitter binds to cardiac (M_2) muscarinic receptor once released from a neuron and brings about immediate response.

At rest both sympathetic and parasympathetic systems are active with parasympathetic

dominance. The actual balance between them is constantly changing in attempt to achieve optimum considering all internal and external stimuli.

There are various factors affecting autonomic regulation of the heart which includes respiration, thermoregulation, blood pressure, cardiac output.

D. HEART RATE VARIABILITY

Heart rate variability is a noninvasive electrocardiographic marker reflecting the activity of the sympathetic and vagal components of the ANS on the sinus node of the heart. It expresses the total amount of variations of both instantaneous HR and RR intervals (intervals between QRS complexes of normal sinus depolarisations).[1]

Analysis of the variability in R-R intervals in the ECG also known as HRV can indicate any imbalances between sympathetic and vagal influences on the heart.

HISTORY:

HRV originally comes from the field of obstetrics where it became common place in maternity wards. In the past, where there was reason to be concerned about the health of an unborn child, doctors would monitor the heart of the foetus by attaching electrodes to the head. Although it was believed that heart rhythm should be even, it was discovered that unborn infants with near perfect rhythm in the intervals between heartbeats were born dead. Unborn infants with a lot of variability in their heart rhythms were born healthy. Later, HRV tests were done in hospitals to see if the same results applied to adults. It was found that as death approaches adults, the intervals between the heartbeats continue to get more even until they die.

1965- Hon and Lee noted foetal distress preceeded by alteration in the interbeat intervals

before any appreciable change in the average heart rate.

1968- Sayers and others focused attention on the existence of physiological rhythms embedded in the beat-to-beat heart rate signal.

1970- Ewings et al. devised a simple bedside test for short term RR difference to detect autonomic neuropathy in diabetic patients.

1977- Wolf et al. first showed the association of higher risk of postinfarction mortality with reduced HRV.

1981- Akselrod et al. introduced power spectral analysis of heart rate fluctuations to quantitatively evaluate beat to beat cardiovascular control.

1996- Task Force was constituted by European Society of Cardiology and North American Society of Pacing and Electrophysiology

Newer method of autonomic function testing is based on the signal processing applied on heart rate variability (HRV) signal. The information available from the time-frequency representation of HRV signals is useful in classifying the subject population into 4 classes namely normal, sympathetic loss, parasympathetic loss and combined losses. The results of earlier studies suggest that the presence of autonomic neuropathy can be clearly detected by short time HRV signal analysis possible in the clinical environment.[1]

For more than two decades short-term power spectral analysis of HRV has been used to assess autonomic control of HR. Recently, it has also been used to stratify the risk of sudden death in subjects with CHF.[2]

MECHANISM/ CAUSE OF HRV

Although automaticity is intrinsic to different cardiac tissues with pacemaker properties, the electrical and contractile activity of the myocardium is largely modulated by the ANS. Both branches of the ANS influence ion channel activity implicated in the regulation of depolarisation of the cardiac pacemaker cells.

In a healthy volunteer, the PNS fibres and the SNS fibres richly innervate the sinoatrial node. Parasympathetic innervations of the heart are mediated by the vagus nerve which causes a decreased firing of the SA node thereby decreasing the heat rate whereas stimulation by the sympathetic fibers causes an increase in the heart rate. Thus the variability in the heart rate is due to the action of balance and synergy between the two branches of the autonomic system, which is mainly enforced through neural, mechanical, humoral and other physiological mechanisms. It maintains cardiovascular parameters in their most favorable ranges and permits suitable reactions to change in external or internal stimuli.[3]

This balance between the effect of the SNS and the PNS is known as the sympathovagal balance and is believed to be echoed in the beat-to-beat changes of the cardiac cycle.[4]

The effect of vagal stimulation on the cardiac pacemaker cells is to cause hyperpolarisation and to reduce the rate of depolarisation, sympathetic stimulation causes chronotropic effects by increasing the rate of pacemaker depolarisation. The SAN responds to vagal activity within one or two heart beats, but its overall effects are relatively shortlived. Vagal induced changes in HR typically occur within 5 s whereas cardiac responses to SNS regulation occur more slowly with initial response delays of up

to 5 s, followed by a progressive change and a maximum response after 20 to 30 s. These differences in response times are due in part to the relatively slow exocytotic release of noradrenaline from sympathetic nerve terminal through which the SNS regulates cardiac activity. Also, unlike PNS acetylcholine mechanisms, a secondary messenger (adenylyl cyclase) is involved in SNS regulation which further slows the process. Ach released from the postganglionic parasympathetic terminal binds to the muscarinic cholinergic receptor and activates transmembrane potassium channel and hence reduces HR. Other anatomical disparities between the autonomic branches may also contribute to the slower response rate associated with SNS regulation. For instance, the preganglionic cell bodies of the PNS neurons are located within the heart itself, whereas those of the sympathetic neurons are comparatively isolated in the paravertebral ganglia. Furthermore, preganglionic fibres are also myelinated contributing to faster electrical transmission of vagal regulatory signals compared to transmission rates in unmyelinated SNS fibres.[5]

Thus, increased HRV shows parasympathetic dominance and reduced HRV indicates sympathetic dominance of the heart.

Hence, HRV analyses the tonic baseline autonomic function. In a normal heart with an intact ANS, there will be continuous physiological variations of the sinus cycles reflecting a balanced sympthovagal state and normal HRV. The changes in activity in the afferent and efferent fibers of the ANS and in the local neural regulation will contribute to the resulting sympathovagal imbalance, reflected by a diminished HRV.

AUTONOMIC FUNCTION TEST:

Cardiovascular autonomic functioning of the heart can be tested by

A. Standard tests devised by Ewings et al.

B. Power Spectral analysis of HRV.

C. Time domain measures of HRV

A. Standard tests of autonomic function test: These are non invasive tests designed by Ewings et al..

Sympathetic Function Tests:

i) BP response to standing.

Record the difference in systolic blood pressures in supine position and after standing for 1 minute.

Interpretation: Normal : <10 mmHg. Borderline: 11-20 mmHg. Abnormal: >30 mmHg.

ii) BP response to sustained handgrip.

Take resting systolic pressure. Maintain handgrip in other arm at 30% of maximum voluntary pressure (use dynamometer) for up to 5 minutes; record systolic pressure each minute. Stop if rise reaches normal level. If not, record rise to just before handgrip release at 5 minutes.

Interpretation: Normal: >16 mmHg. Borderline: 11-15 mmHg. Abnormal: <10 mmHg.

Parasympathetic Function Tests:

iii) HR response to standing.

Attach ECG limb leads. With strip recorder running (lead II), patient stands from lying as quickly as possible. Measure 30:15 ratio i.e. ratio of longest R-R interval around 30^{th} beat after standing to shortest R-R interval about 15 beats after standing.

Interpretation: Normal: >1.04. Borderline: 1.01-1.04. Abnormal: <1.00.

iv) HR response to deep breathing.

With patient sitting and strip ECG recording, patient breathes deeply and evenly at 6 breaths per minutes (5 seconds in; 5 seconds out) for 3 cycles (30 seconds). Count "IN-2-3-4-5-OUT-2-3-4-5-as they do. Measure greatest heart rate difference during each cycle and average the 3 differences.

Interpretation: Normal: >15 beats/min. Borderline: 11-14 beats/min Abnormal: <10 beats/min.

v) HR response to Valsalva.

Pierce the cardboard tube in the middle first with a wide-bore needle to ensure a slow air leak. With patient sitting and strip ECG recording, patient breathes into disposable cardboard mouthpiece attached to aneroid sphygmomanometer to keep pressure at 40 mmHg for 15 seconds. Record for another 30 seconds more. Take ratio of longest R-R interval within 20 beats of ending manoeuvre to shortest interval during manoeuvre. Repeat twice more, and average the ratio from the 3 Valsalva attempts.

Interpretation: Normal: >1.21. Abnormal: <1.20.

Diagnostic criteria:-

Normal	: -	All tests normal, or 1 borderline result.
Mildly Abnormal	: -	One of the 3 HR tests abnormal or 2 borderline.
Definitely abnormal	: -	Two or more of the HR tests abnormal.
Severely abnormal	: -	Two or more of the HR tests abnormal, plus one or both of the BP tests abnormal or both borderline.

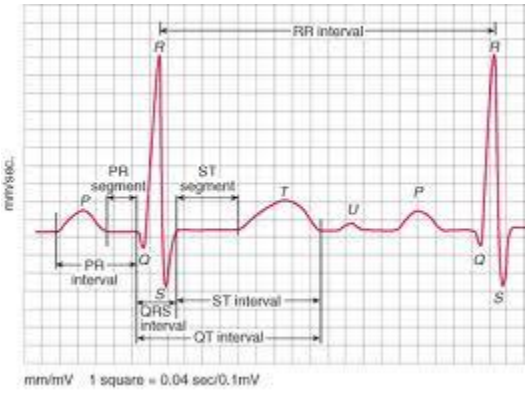
E. MEASURES OF HRV:

HRV can be studied by different methods: mathematical modeling of heart rate regulatory systems; non linear methods for determining indices for regulatory functions; time domain methods to determine the deviation of successive N-N (normal R-R) intervals; spectral domain methods to determine the power spectral density of definitive frequency components of ECG.

ECG:

Electrocardiography is a transthoracic interpretation of the electrical activity of the heart over a period of time, as detected by electrodes attached to the outer surface of the skin and recorded by a device external to the body. The recording produced by this noninvasive procedure is termed an electrocardiogram.

7. An ECG recording



P wave, represents atrial depolarisation. The presence of P waves indicates ‘sinus rhythm’, the heart’s normal rhythm.

PR interval, represents conduction through the AV node and the bundle of His. This should be between 120–200 ms, or less than 5 mm on the ECG paper.

The QRS complex, represents depolarisation of the ventricles. A Q wave is any negative deflection at the beginning of a QRS complex. Small Q waves in some leads may be normal. Large Q waves (> 2 mm) may be abnormal. An R wave is the first positive deflection, and an S wave is the negative deflection immediately following an R wave. The QRS complex should be less than 120 ms (3 mm).

The ST segment, between the end of the S wave and start of the T wave. The ST segment should be 'isoelectric', that is, at the same level as the part between the T wave and the next P wave.

T wave, represents repolarisation of the ventricles.

RR interval- The interval between an R wave and the next R wave . normal- 0.6-1.2s

HRV denotes the variabilities of both consecutive instantaneous HR and consecutive RR intervals. The other terms of HRV are cycle length variability, heart period variability, RR variability, RR interval tachogram.

B. POWER SPECTRAL ANALYSIS OF HRV:

Frequency domain (power spectral density) analysis describes the periodic oscillations of the heart rate signal decomposed at different frequencies and amplitudes; and provides information on the amount of their relative intensity (termed variance or power) in the heart's sinus rhythm. Schematically, spectral analysis may be compared to the results obtained when white light passes through a prism, resulting in different lights of different colour and wave length. Power spectral analysis can be performed in two ways: 1) by a nonparametric method, the fast Fourier transformation (FFT), which is characterized by discrete peaks for the several frequency components, and 2) by a parametric method, the autoregressive model estimation, resulting in a continuous smooth spectrum of activity. While the FFT is a simple and rapid method, the parametric method is more complex and needs verification of the suitability of the chosen model.[1]

When using the FFT the individual RR intervals stored in the computer are transformed into bands with different spectral frequencies. This process is similar to decomposing the sound of a symphony orchestra into the underlying notes. The results obtained can be transformed in Hertz (Hz) by dividing by the mean RR interval length.

The power spectrum consists of frequency bands ranging from 0 to 0.5 Hz and can be classified into four bands: the ultra low frequency band (ULF), the very low frequency band (VLF), the low frequency band (LF) and the high frequency band (HF).[1]

Variable	**Units**	**Description**	**Frequency range**
Total power	ms^2	variance of all NN intervals	<0.4 Hz
ULF	ms^2	ultra low frequency	<0.003 Hz
VLF	ms^2	very low frequency	<0.003-0.04 Hz

LF	ms^2	Low frequency power	0.04-0.15 Hz
HF	ms^2	high frequency power	0.15-0.4 Hz
LF/HF	ratio	ratio of low-high frequency power	

Very Low Frequency Power ms^2

Physiological explanation of VLF is less defined.

It changes with change in temperature and ACE inhibitors.

It is not relevant in 5 min ECG recordings and it is still under study.

Low Frequency Power ms^2

This is an indicator for more sympathetic than parasympathetic modulation and this was proved by the use of beta blockers.

This requires minimum of 2 minutes recording of ECG.

The magnitude of the LF component provides an index of sympathetic activity with vagal modulation.

High Frequency Power ms^2

This power spectral oscillation is seen only for parasympathetic nervous system.

It is specially blocked by parasympatholytic drugs.

Even 1 minute ECG recording is enough to assess this power.

The magnitude of the HF component provides an index of vagal activity.

LF/HF

LF/HF ratio has been used as a non-invasive index of sympathovagal balance. Interpretation of these indices depends upon the existing physiological state. It is dimensionless.

Normalization of units (nu)

LF (nu), HF (nu) are the normalization of powers which gives near 100% values of the sympathetic and parasympathetic events. They are calculated as follows:

LF (nu) = LF Power/ (LF+HF) Power or LF Power/ (TP-VLF) Power

HF (nu) = HF Power/ (HF+LF) Power or HF Power/ (TP-VLF) Power

Total Power (TP) is the summation of LF+HF Power.[2]

C. TIME DOMAIN MEASURES:

Time domain analysis measures the changes in heart rate over time or the intervals between successive normal cardiac cycles. In a continuous ECG recording, each QRS complex is detected and the normal RR intervals (NN intervals), due to sinus depolarisations, or the instantaneous heart rate, are then determined.

There are 2 time domain measures.

a. statistical methods,

b. geometric methods

a. Statistical methods:

The calculated time domain variables may be simple, such as the mean RR interval, the mean heart rate, the difference between the longest and shortest RR interval, or the difference between night and day heart rate; and more complex based on statistical measurements. These statistical time domain indices are divided in two categories, including beat-to-beat intervals or variables derived directly from the intervals themselves or the instantaneous HR and intervals derived from the differences between adjacent NN intervals.

SDNN (Standard Deviation of all NN intervals) –

It is a global index of HRV and reflects all long-term components and circadian rhythms responsible for variability in the recording period. It is the most stable score in HRV and the measure of variability itself. SDNN is the score used to predict mortality as shown by several risk predictive values of HRV measures in selected outcome studies. Elaborate studies on predicting death with various medical indices found that a **reduction of SDNN was the most powerful predictor of risk of death** due to cardiovascular morbidity and that it is a better predictor of death than other conventional clinical measurements.[6]

Reduced HRV is indicated by reduced SDNN.

SDANN (standard deviation of the averages of NN intervals in all 5-minute segments of the entire recording) -

It is an index of the variability of the average of 5-minute. Thus, it provides long-term information. It is a sensitive index of low frequencies like physical activity, changes in position, circadian rhythm.

SD (standard deviation of differences between adjacent NN intervals)-

It is generally considered to reflect the day/night changes of HRV.

RMSSD (square root of the mean of the sum of the squares of differences between adjacent NN interval) and pNN50 (percent of difference between adjacent NN intervals that are greater than 50 ms) -

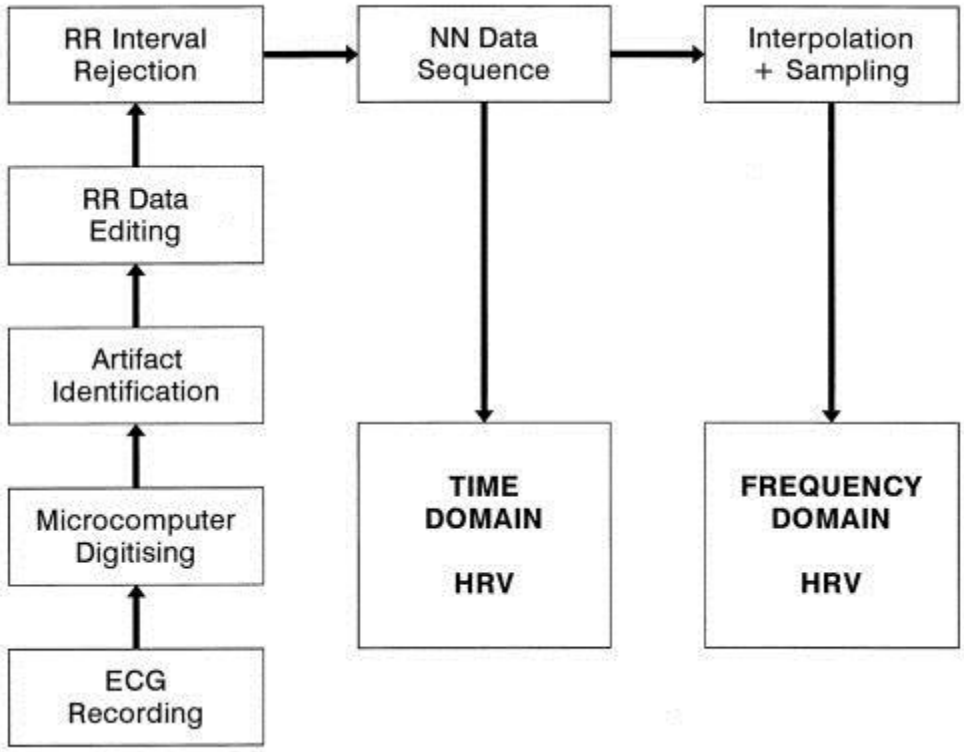
They are the most common parameters based on interval differences. These measurements correspond to short-term HRV changes and are not dependent on day/night variations. They reflect alterations in autonomic tone that are predominantly

vagally mediated. Compared to pNN50, RMSSD seems to be more stable and should be preferred for clinical use.

b. Geometric methods:

Geometric methods are derived and constructed from the conversion of sequences of NN intervals. There are different geometrical forms for assessing HRV: the histogram, the HRV triangular index and its modification, the triangular interpolation of NN interval histogram, and the method based on Lorentz or Poincaré plots. The histogram assesses the relationship between the total number of RR intervals detected and the RR interval variation. The triangular HRV index considers the major peak of the histogram as a triangle with its baseline width corresponding to the amount of RR interval variability, its height corresponds to the most frequently observed duration of RR intervals, and its area corresponds to the total number of all RR intervals used to construct it. The triangular HRV index is an estimate of the overall HRV.[1]

REPRESENTATION OF THE CIRCUIT INVOLVED IN HRV RECORDING[7]



F. PHYSIOLOGICAL FACTORS REGULATING HRV:

1. Age: Sympathetic activity increases and parasympathetic activity decreases progressively with aging. The plasma concentration of norepinephrine, as well as efferent sympathetic nerve traffic to skeletal muscle shows an increase with age. In spectral analysis of HRV, a decrease in both LF and HF bands with increasing age has been demonstrated.[8]

2. Blood Pressure: Lower HRV, reduced vagal tone and higher sympathetic function are associated with higher values of blood pressures putting subjects with such trends at a higher risk of developing hypertension.[9]

3. Renin Angiotensin Aldosterone system: it interacts with the autonomic control of the heart. Angiotensin II increases the central sympathetic tone and facilitates norepinephrine release from sympathetic nerve terminal thus reducing HRV. Also, aldosterone brings about a sympathoexcitatory effect by inhibiting the synthesis of Nitric Oxide.

4. Respiratory sinus arrhythmia: Respiratory sinus arrhythmia is a naturally occurring variation in heart rate that occurs during a breathing cycle. Heart rate increases during inhalation and decreases during exhalation.[10]

5. Thermoregulation: On exposure to cold, there is sympathetic activation thus enhancing release of catecholamines and reducing HRV. On exposure to heat, there is inhibition of sympathetic nervous system thus enhancing HRV.

6. Neuroendocrine secretion: stimulation of neuroendocrine cell for eg, adrenal medullary cell leads to increased sympathetic stimulation which in turn leads to reduced HRV.

7. Circadian rhythms: ANS changes during sleep include an increase in parasympathetic tone and a decrease in sympathetic activity during NREM sleep. It is reflected by increased HRV during NREM sleep. REM sleep is characterized by further increase in parasympathetic tone and further decrease in sympathetic activity, but intermittently there is an increase of sympathetic activity during phasic REM sleep and this is reflected by reduced HRV.

G. CLINICAL IMPLICATIONS OF HRV:

Altered HRV indicates sympathovagal imbalance of the heart. It is found that lowered HRV is associated with aging, decreased autonomic activity, hormonal tonus, specific types of autonomic neuropathies (e.g. diabetic neuropathy) and increased risk of sudden cardiac death after acute MI.

The mainly common pathway of sudden cardiogenic death is cardiac neural dysregulation. This could be conveniently screened and monitored by heart rate variability spectral analysis.

Established clinical data based on numerous studies published during the last decade consider decreased global HRV as a strong predictor of increased all-cause cardiac and/or arrhythmic mortality, particularly in patients at risk after MI or with CHF.

Other research indicated that depression, panic disorders and anxiety have negative impact on autonomic function, typically causing depletion of parasympathetic tonus.[11]

On the other hand an increased sympathetic tonus is associated with lowered threshold of ventricular fibrillation. These two factors could explain why such autonomic imbalance caused by significant mental and emotional stress increases risk of acute MI followed by sudden cardiac death.[12]

There are several pathological conditions leading to altered HRV. Few of the conditions include diabetes mellitus, orthostatic hypotension, Parkinsonism, Sleep disorders, Attention Deficit Hyperactive Disorder, Multiple Sclerosis, Migraine, Polyneuropathy, Myasthenic syndromes (Eaton Lambert), chronic fatigue syndrome, hypertension, bipolar diseases and morbid obesity.

Aside from that, there are multiple studies indicating that HRV is quite useful as a

way to quantitatively measure physiological changes caused by various interventions both pharmacological and non-pharmacological during treatment of many pathological conditions having significant manifestation of lowered HRV.

However it is important to realize that clinical implication of HRV analysis has been clearly recognized in only two medical conditions[13]:

i. Predictor of risk of arrhythmic events or sudden cardiac death after acute MI.

ii. Clinical marker of diabetic neuropathy evolution.

Nevertheless, as the number of clinical studies involving HRV in various clinical aspects and conditions grows, HRV remains one of the most promising methods of investigating general health in the future.

Cigarette smoking is also an important factor causing reduced HRV.

H. CIGARETTE SMOKING AND HRV –

Cigarette smokers are exposed to nicotine directly. This nicotine has complex and often unpredictable effect on the various systems of the body. The ultimate response of any one system represents the summation of stimulatory and inhibitory effect of nicotine. In cardiovascular system, it causes increase in heart rate by excitation of the sympathetic or paralysis of the parasympathetic cardiac ganglia, or it can slow heart rate by paralysis of the sympathetic and stimulation of the parasympathetic cardiac ganglia. In addition, the effects of nicotine on chemoreceptors of the carotid and the aortic bodies and on the brain centres influence heart rate. Nicotine also elicits a discharge of epinephrine from the adrenal medulla which accelerates heart rate and raises BP.[14]

When administered intravenously to the dogs, nicotine characteristically produces

an increase in heart rate and BP. The latter is usually more sustained. In general, the cardiovascular responses to nicotine are due to stimulation of sympathetic ganglia and adrenal medulla, together with discharge of catecholamines from the sympathetic nerve endings.[14]

DEMOGRAPHICS:

According to WHO figures, smoking is responsible for approximately 5 million deaths worldwide every year. Tobacco smoking is a known or probable cause of approximately 25 diseases and even WHO says that its impact on the world health is not fully assessed. By 2020, tobacco-attributable mortality is projected to increase 8.4 million that is approximately 9% of the worldwide mortality burden.[15] There is believed to be 1.1 billion smokers in the world, 800 million of them in developing countries.[17] There are approximately 120 million smokers in India, about 37% of all men and 5% of all women.[16]

Pandemic of smoking related death and disease is poised to claim a million lives each year in India. Smoking among persons between ages 30 and 69 is responsible for about 1 in 20 deaths of women and 1 in 5 deaths of men in India and that by 2010 smoking will cause about 930,000 adult deaths (annually) in India.[15]

Tobacco deaths is said to rise to around 10 million deaths annually during the 2020s or 2030s. Of the latter figure, 7 million deaths will occur in developing countries. In Karnataka, tobacco use has reached a prevalence of 41% among men and 14.9% among women.[15]

EFFECT OF CIGARETTE SMOKE ON HRV:

Smoking causes an acute and transient decrease in vagal cardiac control and that heavy smoking causes long-term reduction in vagal cardiac control in young people and blunted postural responses in autonomic cardiac regulation.[18] Following smoking, there is increased plasma levels of epinephrine and norepinephrine leading to sympathetic dominance and blunted parasympathetic responses. This is seen as reduced HRV.[18,22]

Smoking is also known to promote damage to endothelium, accelerated atherosclerosis, adverse changes in lipid profile which are important risk factors in the pathophysiology of hypertension.[19]

Exposure to environmental tobacco smoke showed an association with lowered HRV and higher heart rate in a population based study showing that even passive smokers where at increased risk of autonomic imbalance due to tobacco smoke.[20,21]

Study done in Turkey suggested that HRV was lower in people who smoked 10 cigarettes per day or more, than in the nonsmoker group or people who smoke fewer than 10 cigarettes per day. Further, it also showed that cigarette smoking acutely increased plasma catecholamine and cardiac norepinephrine spillover and resulted in increase in blood pressure, heart rate and sympathetic outflow. Chronic smokers have higher pulse rate and blood pressure compared with nonsmokers indicating sympathetic hyperactivity and reduced HRV.[22]

HRV analysed on smokers after acute MI showed that although smoking reduces HRV in general population, higher HRV was observed in smokers than nonsmokers after acute MI under the condition of smoking cessation.[23]

OTHER EFFECTS OF CIGARETTE SMOKING:

Tobacco is the single greatest cause of preventable death globally according to a WHO report. It contains about 4000 chemicals. Many more toxic chemicals are formed when it is burning including atleast 250 chemicals known to be toxic or capable of causing cancer.

Tobacco use leads most commonly to diseases affecting the heart and lungs, with smoking being a major risk factor for heart attacks, strokes, chronic obstructive pulmonary disease (COPD) (including emphysema and chronic bronchitis) and cancer (particularly lung cancer, cancers of the larynx and mouth and pancreatic cancer). It also causes peripheral vascular disease and hypertension. These effects depend on the number of years that a person smokes and on how much the person smokes. Starting smoking earlier in life and smoking cigarettes higher in tar increases the risk of these diseases. Cigarettes sold in underdeveloped countries tend to have higher tar content and are less likely to be filtered, potentially increasing vulnerability to tobacco-related disease in these regions. Conventional cigarette smoke in India contains tar- 11 mg and nicotine – 0.8mg.

Cigarette smoke related cardiovascular dysfunctions are largely unknown, but it increases inflammation, thrombosis and oxidation of low-density lipoprotein cholesterol. Recent experimental and clinical data support the hypothesis that cigarette smoke exposure increases oxidative stress as a potential mechanism for initiating cardiovascular dysfunction.[24]

Nicotine markedly stimulates CNS causing alertness and faster reaction times. The stimulatory, pleasure reward, reinforcement and enhanced working memory actions of

the nicotine appear to result from the release of excitatory amino acid, dopamine and other biogenic amines from the CNS centres.[25,26]

I. CESSATION OF SMOKING AND HRV:

There is overwhelming evidence demonstrating both the cardiovascular hazards of smoking and the prompt benefit that occurs with smoking cessation.

When the resting HRV following cessation of smoking for 12 hours in young and old smokers in a study done in India was tested it was found to be comparable with that of nonsmokers.[27]

Smokers who desired to quit attended smoking cessation classes and used transdermal nicotine patches while abstaining from smoking. After 4 to 6 weeks of using 21 mg patches, there was significant increase in HRV. Four weeks after cessation of patch use, there was significant decrease in heart rate, and increase in all 24-hour time and frequency domain indexes of HRV. Part of this change occurred in the transition from smoking to the patch, and further changes occurred with cessation of patch use patch use.[28]

The effects of cigarette smoking and smoking cessation on cardiac neural regulation in a group of male adult schizophrenic patients was studied. The results suggested that the habitually-smoking schizophrenic patients, as compared to the nonsmoking patients, manifested further cardiac neural dysregulation, including decreased total autonomic function activity, slightly increased sympathetic outflow and impaired parasympathetic function activity which could be somewhat reversed by smoking cessation.[29]

HRV was analysed during the first month of smoking cessation.One day after smoking cessation, heart rate decreased significantly, and all 24-hour time and frequency domain indices of HRV increased. The magnitude of increase in these indices peaked 2 to 7 days after smoking cessation and gradually decreased thereafter. The increase in HRV persisted 1 month after smoking cessation.[30]

The provision of advice alone significantly increases the smoking cessation rate and even minimal counseling yields a further benefit.

Numerous prospective investigations have demonstrated a substantial decrease in CHD mortality for former smokers compared with continuing smokers.[31] This diminution in risk occurs relatively soon after cessation of smoking and increasing intervals since the last cigarette smoked are associated with progressively lower mortality rates from CHD.[32] Similar rapid decrease in risk with smoking cessation are also seen for ischemic stroke.[33,34]

Benefits from quitting are seen in former smokers even after many years of heavy smoking. Investigations also have demonstrated benefits from cessation for smokers who have already developed smoking-related diseases or symptoms. Persons with diagnosed CHD experience as much as a 50% reduction in risk of reinfarction, sudden cardiac death and total mortality if they quit smoking after the initial infarction.[35,36]Furthermore, the patient who has recently developed a clinical illness is very motivated to change and several studies have shown that intervention in this "teachable moment" can be very effective. Thus, the provision of smoking cessation advice is associated with a 50% long-term (more than 1 year) smoking cessation rate in patients who have been hospitalized with a coronary event and even modest telephone-based counseling can increase this

percentage to ≥70% in a particularly cost-effective manner.[37,38]

Meanwhile, earlier studies showed that there is an increase in HRV following quitting smoking attempt using drugs like nicotine replacement therapy.[39]

The smoking status of all patients should be assessed and appropriate intervention offered to those who smoke. Physicians should be trained in counseling techniques and the use of nicotine replacement therapy. The importance of ensuring the delivery of smoking cessation counseling was recognized when smoking counseling assessments were incorporated into version 3 of HEDIS, the Health Plan Employer Data Information Set of the National Committee for Quality Assurance. Equally important components of appropriate medical care are development of supportive office systems and multicomponent intervention programs and links with smoking cessation specialists and community resources.[40]

METHODOLOGY

MATERIALS AND METHODS

SOURCE OF DATA

The study group comprised of 35 smokers and 35 age and gender matched non smokers who volunteered for the study and also those smokers who volunteered to quit smoking for duration of one week subsequently.

SELECTION OF SUBJECTS

The subjects were recruited based on various inclusion and exclusion criteria from teaching and non teaching staff of Sri Devaraj Urs Academy of Higher Education and Research and from attenders of patients attending R L Jalappa Hospital, Kolar after taking informed consent. Ethical clearance for the study was obtained from the Institutional Ethical Committee.

CRITERIA FOR SELECTION OF STUDY GROUP

Inclusion criteria :

Study group:

1. Male subjects between 18-50yrs of age.
2. Subjects should be smokers.

Control group:

1. Male subjects between 18-50yrs of age.
2. The subjects should be nonsmokers.

Exclusion criteria:

1. Subjects with history of diabetes mellitus, hypertension.
2. Subjects with history of myocardial infarction
3. Subjects with history of anxiety disorders.

4. Subjects on medication with antiarrhythmics and atropine.

5. Subjects with history of Guillian barre syndrome, multiple sclerosis and Parkinsonism.

METHODOLOGY

The subjects were selected based on inclusion and exclusion criteria. After taking informed consent of the subjects, information was collected about their smoking history.

Pack years of smoking is defined as the number of packs (one pack=20 cigarettes) smoked per day multiplied by the duration of smoking in years.

A general physical and systemic examination was conducted. The instrument used in this study was portable ECG system CARDIART 8408 VIEW. A high quality ECG recording was taken under standardized conditions to minimize artifacts. Analysis of this was done using time domain method. Recording was done in the morning hours between 9:00a.m and 11:00a.m.

The subjects were given the following instructions.

- To avoid food two hours prior to testing
- To avoid coffee or alcohol 24 hours prior to testing
- To wear loose and comfortable clothing during the test

Recording: The electrocardiogram (ECG) was recorded in the supine position for 5 minutes after 10 minutes of supine rest. The analog ECG signal was obtained using lead two. Subjects were instructed to close the eyes and to avoid talking, moving of hands, legs and body, coughing and sleeping during the test.

Acquisition: The ECG signal was continuously amplified, digitized and analysis was obtained. The RR peak detector was adjusted appropriately. The data obtained was

analyzed and the following parameter was recorded:

Time domain measure: SDNN(s)

The study group were counseled to quit smoking for one week and asked to come for repeat HRV after one week. In a similar way HRV recording and analysis was performed. The control group was also instructed to come after one week for repeat HRV recording.

HEART RATE VARIABILITY MACHINE- CARDIART 8408 VIEW

RECORDING OF HEART RATE VARIABILITY

RESULTS AND ANALYSIS

RESULTS & ANALYSIS

In the present study, 35 smokers (study group) and 35 age and gender matched controls who were non smokers were selected considering the inclusion and exclusion criteria and were subjected to Heart Rate Variability recordings. The data was analysed using appropriate statistical methods and discussed below.

Presentation of data:

Master chart showing age, pack years of smoking and SDNN (time domain HRV recording) of the subjects and SDNN recorded after cessation of smoking for 1 week. SDNN of controls at baseline and after one week was also tabulated.

Statistical Treatment of the data:

The data was suitably arranged into tables for discussion under different headings. Descriptive statistical analysis was carried out on this data. Results on continuous measurements are presented as mean $\pm$ standard deviation and results on categorical measurements are presented in number%. Significance was assessed at 5% level of significance. HRV recording was compared between smokers and age matched controls using independent student't' test. SDNN of smokers before cessation and after cessation was compared using paired student't' test. The Pearson correlation between pack years of smoking and SDNN was also done. Conclusions are drawn based on the outcome of this statistical treatment.[41,42]

RESULTS AND ANALYSIS:

Table 1: Mean age of subjects studied

	STUDY GROUP (n=35)	**CONTROLS (n=35)**	**INDEPENDENT t TEST 'p' VALUE**
MEAN AGE ± SD (YRS)	39.57± 5.97	36.57 ± 8.85	0.101

Table 1 shows mean± SD of age of study group as 39.57±5.97 years and that of controls being 36.57±8.85years which is not significant with a p value of 0.101.

Graph 1: Mean age of subjects studied

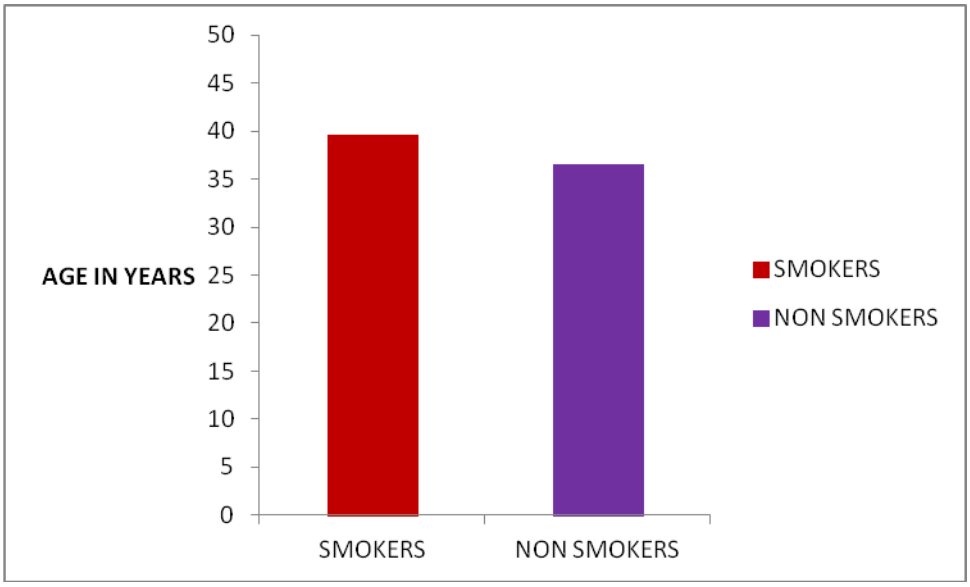


Table 2: Duration of Smoking in years

Duration of smoking	**Number of subjects**	**%**
1-10 years	9	25.7
11-20 years	15	42.9
21 years & above	11	31.4
Total	35	100.0

Mean ± SD: 17.49±7.13

Table 2 shows distribution of duration of smoking in percentage of the study group in years. Mean ± SD of duration of smoking was 17.49±7.13 years.

Graph 2: Duration of Smoking in years

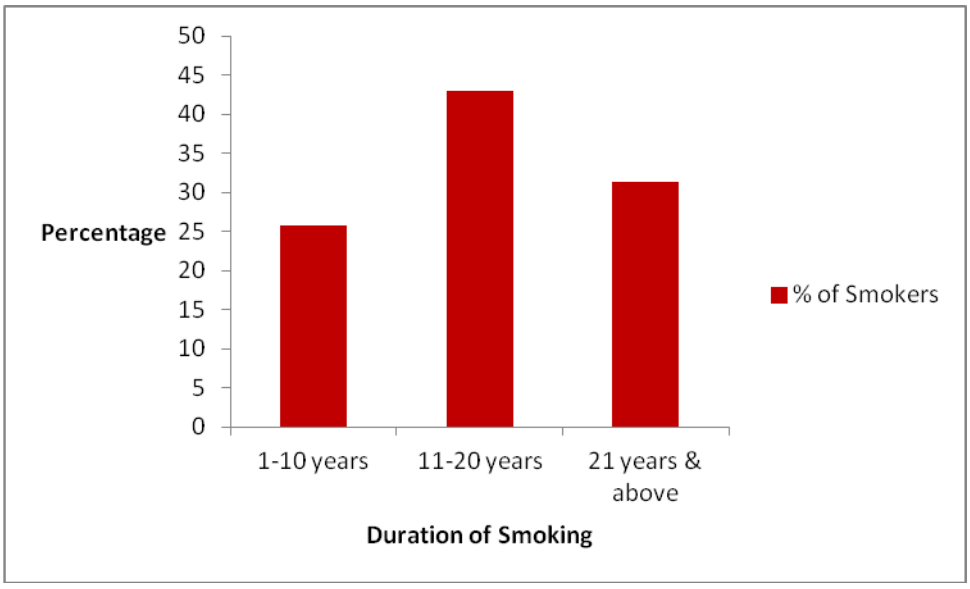


Table 3: Number of cigarettes smoked per day

Number of cigarettes per day	**Number of subjects**	**%**
1-10	13	37.1
11-20	16	45.7
21-30	4	11.4
Total	35	100.0

Mean ± SD: 14.74±6.02

Table 3 shows distribution of study group in percentage according to number of cigarettes smoked per day. Mean ±SD of number of cigarettes smoked per day was 14.74±6.02

Graph 3: Number of cigarettes smoked per day

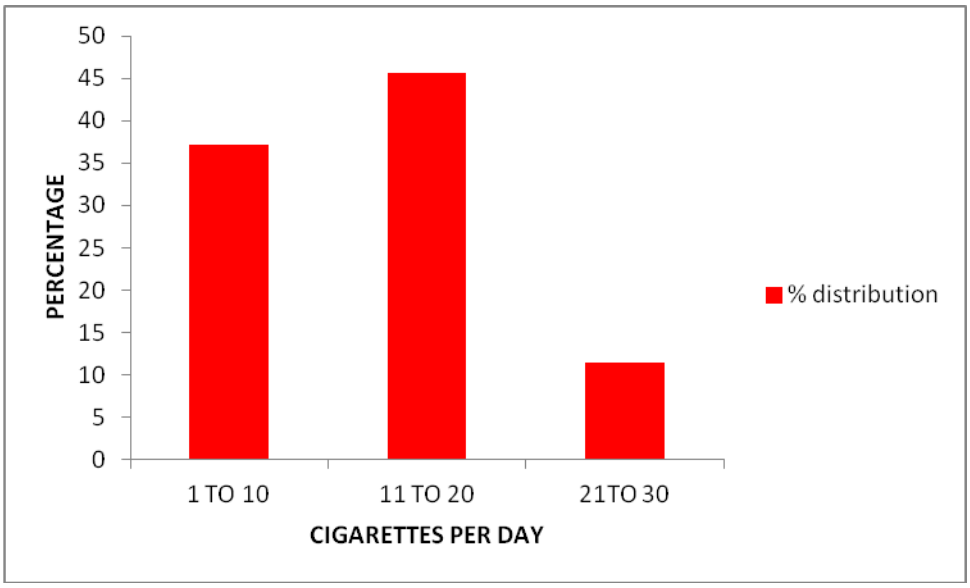


Table 4: Number of pack years

Number of pack years	Number of subjects	%
1-10	18	25.7
11-20	10	14.3
21 years & above	7	10.0
Total	35	100.0

Mean ± SD: 13.33±8.81

Table 4 shows distribution of study group in percentage according to pack years of smoking. Mean ± SD of pack years of smoking was 13.33±8.81.

Graph 4: Number of pack years

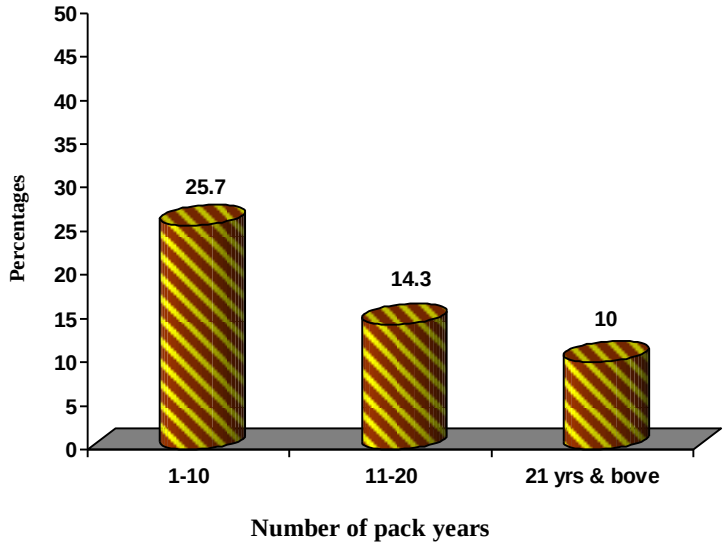


Table 5: Comparison of SDNN of study group and controls

	STUDY GROUP	**CONTROLS**	**INDEPENDENT 't' TEST 'p' VALUE**
SDNN (s)	0.0531±0.053	0.0815±0.032	0.009***

Table 5 shows comparison of SDNN of study group and controls by applying independent't' test. There was a significant reduction of SDNN among study group as compared to controls with a p value of 0.009.

Graph 5: Comparison of SDNN of study group and controls

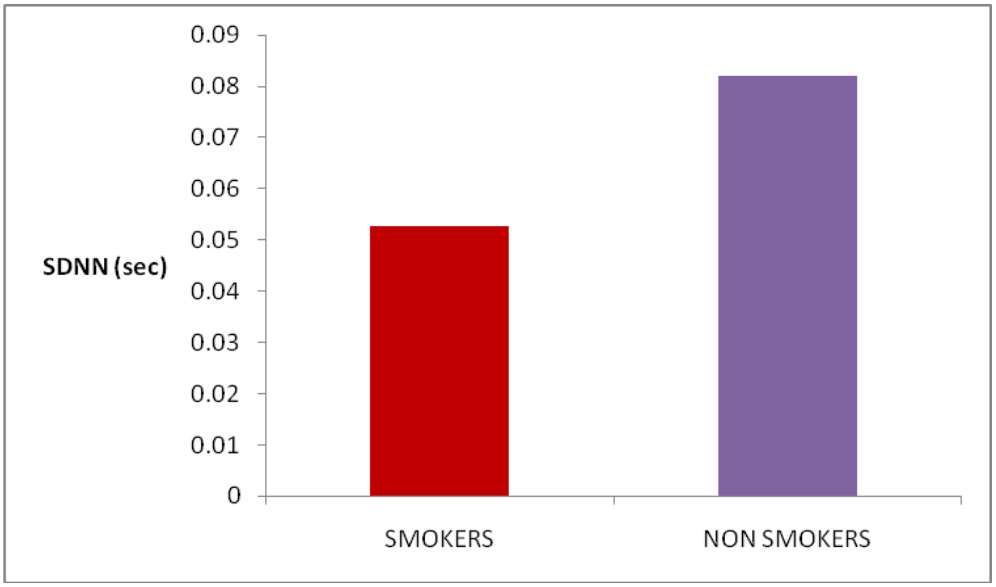


Table 6: Comparison of SDNN of study group during and on cessation of smoking (n=35)

	STUDY GROUP BASELINE	**ON CESSATION OF SMOKING**	**PAIRED 't' TEST p VALUE**
SDNN (s)	0.0531±0.053	0.0766±0.023	<0.005**

Table 6 shows comparison of SDNN of study group during and after cessation of smoking for 1 week by applying paired 't' test. There was a significant increase in SDNN after cessation of smoking with a p value of <0.005.

Graph 6: Comparison of SDNN of study group during and after cessation of smoking

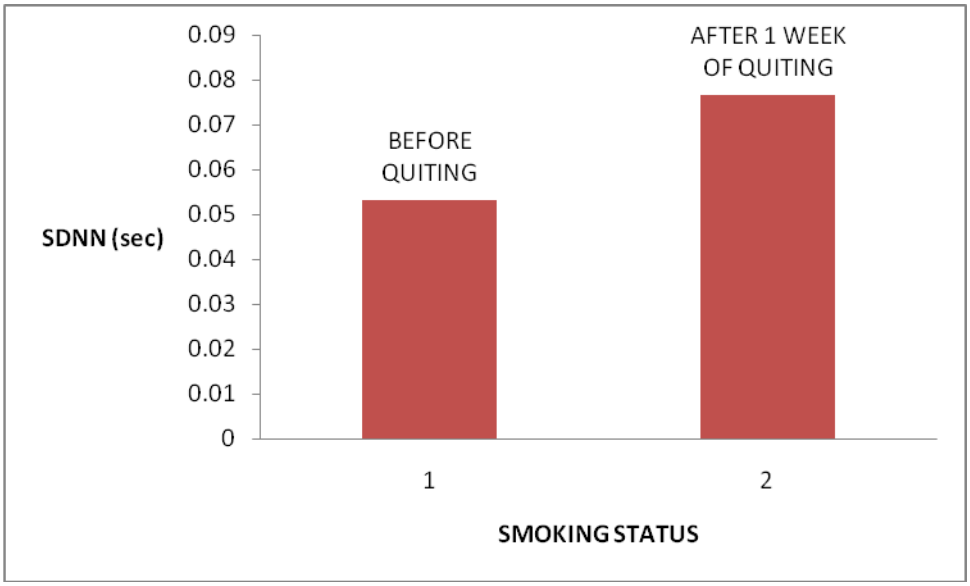


Table 7: Comparison of SDNN of controls one week apart (n=35)

	NON SMOKERS BASELINE	**AFTER 1 WEEK**	**PAIRED 't' TEST p VALUE**
SDNN(s)	0.081±0.032	0.079±0.023	0.334

Table 7 shows comparison of SDNN of controls one week apart by applying paired 't' test. There was no significant difference between the two recording of SDNN among controls with a p value of 0.334.

Graph 7: Comparison of SDNN of controls one week apart

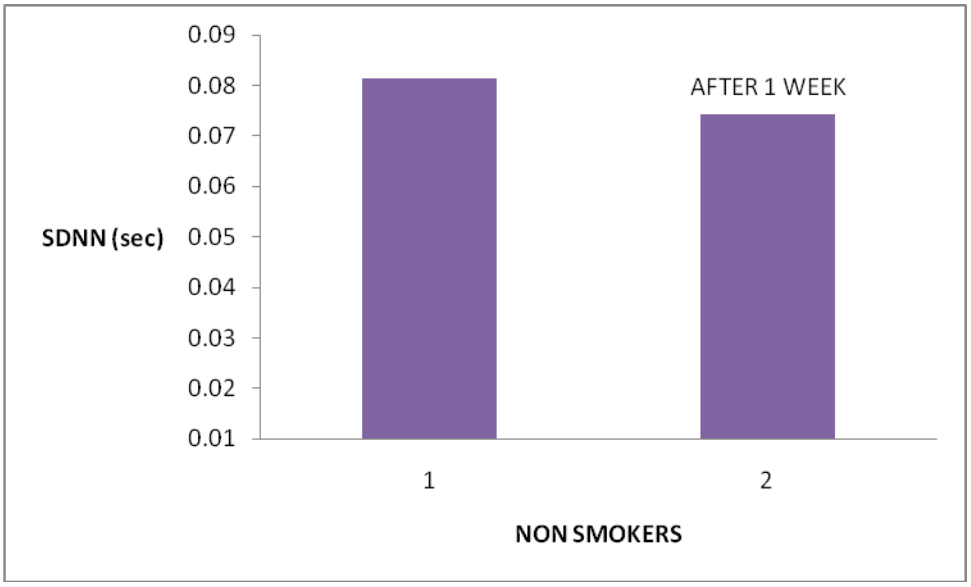
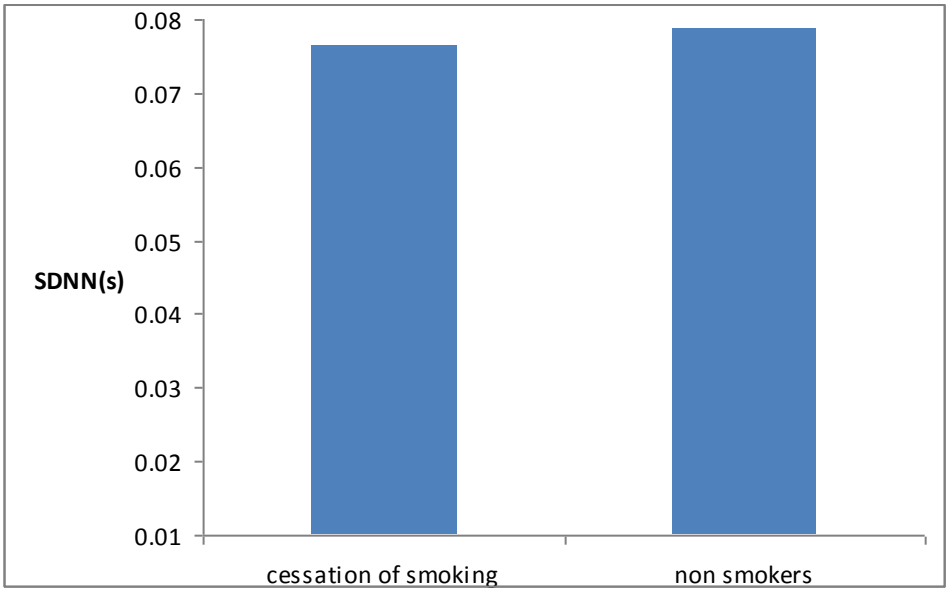


Table 8: Comparison of SDNN of study group after cessation of smoking and of controls

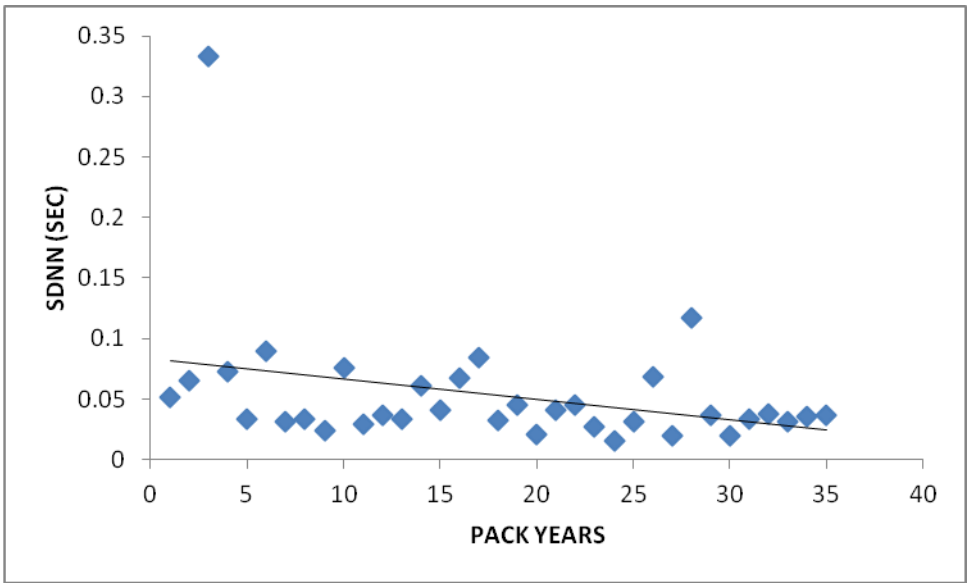
	STUDY GROUP AFTER QUITTING	**CONTROLS**	**INDEPENDENT 't' TEST p VALUE**
SDNN (s)	0.0766±0.023	0.079±0.023	0.608

Table 8 shows comparison of SDNN of study subjects after quitting smoking and controls by applying unpaired 't' test. There was no significant difference between their SDNN with a p value of 0.608.

Graph 8: Comparison of SDNN of study group after cessation of smoking and of controls



Graph 9: PEARSON'S CORRELATION:



Pearson's correlation was applied between pack years of smoking and SDNN of study group and there was a negative correlation with r = -0.09 which was not significant with p value of 0.607 .

DISCUSSION

DISCUSSION

Cigarette smoking is injurious to health. Among its several ill effects, hazards to the cardiovascular system are also an important cause of morbidity and mortality.

Deleterious health outcomes associated with reduced cardiac autonomic function, as measured by time-domain measures of HRV, has been well established. It has been used as a prognostic marker in predicting the morbidity and mortality due to altered sympatho-vagal balance of the heart.[43]

SDNN which is a time domain measure of HRV has been used as the parameter to quantify HRV signals in our study. Reduced SDNN depicts reduced HRV thus indicating the altered sympatho- vagal balance with a shift towards sympathetic dominance. SDNN is an indicator of total power. It is the score used to predict mortality as shown by several risk predictive values of HRV measures in selected outcome studies. Elaborate studies on predicting death with various medical indices found that a reduction of SDNN was the most powerful predictor of risk of death due to cardiovascular mortality than other conventional clinical measurements.[6]

Most of the studies related to smoking have been concentrated on power spectral analysis. Very few deal with time domain measure of HRV and cigarette smoking. Hence we decided to use time domain measure of HRV in an attempt to study the sympatho-vagal imbalance due to smoking and the changes observed after cessation of smoking.

It has been shown that there is a reduction in HRV with increase in age.[44] So age matched controls were selected for the study. The mean duration of smoking of our study

group was 17.49±7.13 years with average number of cigarettes smoked per day being 14.74±6.02.

Our study showed that there was significant reduction in SDNN of smokers as compared to that of non smokers with SDNN of smokers being 0.0531±0.053s whereas that of controls being 0.0767±0.023s. This showed that there was significant reduction in HRV and hence cardiovascular sympathetic dominance. A few investigators have shown that HRV is lower in smokers than in nonsmokers on the basis of a cross-sectional comparison of habitual smokers and nonsmoking controls.[18,23] Our finding is in line with the well-established view that smoking increases sympathetic outflow to the heart and blunts parasympathetic response of the heart. In humans the sympathetic activation induced by cigarette smoking probably depends on an increased release and/or a reduced clearance of catecholamines at the neuroeffector junctions.[18,23] It has also been suggested that a smoking-associated impairment of the baroreflex ability to counteract peripheral adrenergic stimulation participates in the sympathoexcitatory effects of smoking in humans.[45] The present study supports these earlier findings.

When investigators tried to find an association between number of cigarettes smoked and HRV, they concluded that HRV was lower in people who smoked 10 cigarettes per day or more, than in the nonsmoker group or people who smoke fewer than 10 cigarettes per day. They also found that chronic smokers have higher pulse rate and blood pressure compared with nonsmokers indicating sympathetic hyperactivity and reduced HRV. In addition, they observed that Vagal modulation of the heart was blunted in them, particularly during a parasympathetic maneuver.[22]

Exposure to environmental tobacco smoke also showed an association with

lowered HRV and with higher heart rate in a population based study. Thus passive smokers also suffer from cardiac autonomic dysregulation, which may be an intermediate step in the pathway to cardiac instability.[20,21]

There is an increase in HRV following cessation of smoking and this has been documented in literature at various time frames of quitting smoking. In our study, we found a significant increase in SDNN of smokers after they quit smoking for duration of 1 week indicating increase in HRV thus implying reduction in sympathetic activity or an augmentation of parasympathetic activity or both. Further studies need to be done to determine the persistence of effect of quitting smoking on HRV.

A study found an increase in HRV within 3 days of reduced exposure to cigarette smoke.[46]In a similar study where smokers quit smoking for a period of 1 week showed that there was a significant decrease in blood pressure, heart rate and plasma norepinephrine and epinephrine levels during the non smoking period which demonstrated the substantial and immediate benefits of smoking cessation on this cardiovascular indices.[47]

There are some concerns about the time-related effect on the measures of HRV. Literature shows that when all time and frequency domain indices of HRV was assessed after a 4 week cessation of smoking, they were significantly elevated, although the LF/HF ratio was not affected. In contrast, it was also shown earlier that in a smaller number of subjects whose HRV was analysed during the first month of smoking cessation, there was a significant increase in HRV within 24 hours and the magnitude of increase in HRV peaked 2 to 7 days after smoking cessation and gradually declined thereafter.[30]

Also, studies have reported that the smoking cessation significantly decreased both pNN50 and the HF component throughout a 24-hour period, indicating that in habitual smokers, parasympathetic nervous function is impaired even in the nighttime when they are sleeping and do not smoke cigarettes. As for the effect of smoking cessation on sympathetic activity in these subjects, plasma norepinephrine and epinephrine were lower in the nonsmoking period than in the smoking period.[47]

Further, a study done on people who abstained from smoking for a period of 6 months showed an improvement in cardiovascular disease risk parameters like plasma fibrinogen levels, reactive capillary flow, haematocrit and reduction in WBC count.[48]

A prospective cohort study showed that the risk of cigarette smoking on total mortality among former smokers decreases nearly to that of never smokers 10 to 14 years after cessation.[49]

HRV analysed on smokers after acute MI showed that although smoking reduces HRV in general population, higher HRV was observed in smokers than nonsmokers after acute MI under the condition of smoking cessation.[23]

All the above studies indicate that the autonomic dysfunction caused due to smoking can be reversed by cessation of smoking.

Smokers who desired to quit attended smoking cessation classes and used transdermal nicotine patches while abstaining from smoking. After 4 to 6 weeks of using 21 mg patches, there was significant increase in HRV. Four weeks after cessation of patch use, there was significant decrease in heart rate, and increase in all 24-hour time and frequency domain indexes of HRV. Part of this change occurred in the transition from smoking to the patch, and further changes occurred with cessation of patch use.[28]

The effects of cigarette smoking and its cessation on cardiac neural regulation in a group of male adult schizophrenic patients were studied. The results suggested that the habitually-smoking schizophrenic patients, as compared to the nonsmoking patients, manifested further cardiac neural dysregulation, including decreased total autonomic function activity, slightly increased sympathetic outflow and impaired parasympathetic function activity which could be somewhat reversed by smoking cessation.[29]

Our study further showed that, not only was there a significant increase in HRV in study group following quitting of smoking but also, the improvement was comparable to that of non smokers.

It was similarly shown that the resting HRV following cessation of smoking for 12 hours in young and old smokers in a study done in India to be comparable with that of nonsmokers.[27]

We also tried to find a correlation between the duration of smoking and HRV. There was a negative correlation which was not significant. This finding verified the substantial and immediate beneficial effects of smoking cessation on the cardiovascular indices. The clinical implications seem to be quite favourable even for individuals who have been long-term cigarette smokers.

SUMMARY AND CONCLUSION

SUMMARY

This study was conducted in the Department of Physiology, Sri Devaraj Urs Medical College, Kolar, to evaluate the effect of cigarette smoking and its cessation on heart rate variability. 35 smokers and 35 age matched controls were subjected to heart rate variability analysis. Statistical analysis revealed that smokers had significantly reduced HRV as compared to controls. Within the study group, on cessation of smoking for a period of 1 week, there was a significant increase in HRV which was comparable to that of non smokers. Also, there was no significant correlation between pack years of smoking and HRV of the study group. Thus, HRV analysis might serve as a useful tool in demonstrating the immediate and substantial benefits of quitting cigarette smoking.

CONCLUSIONS

1. HRV of smokers was significantly reduced as compared to that of non smokers.
2. HRV of smokers measured after they quit smoking for 1 week showed a significant increase.
3. Whereas there was no significant difference in the HRV of non smokers measured 1 week apart.
4. The increase in HRV among smokers after quitting smoking was comparable to that of non smokers.
5. There was no significant correlation between the pack years of smoking and HRV of smokers. This finding verified the substantial and immediate beneficial effects of smoking cessation on the cardiovascular indices. The clinical implications seem to be quite favorable even for individuals who have been long-term cigarette smokers.

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ANNEXURES

A. PROFORMA FOR QUESTIONNAIRE

1. NAME:
2. AGE:
3. ADDRESS:
4. CONTACT NUMBER:
5. OCCUPATION:
6. DO YOU HAVE HISTORY OF DIABETES MELLITUS: YES/NO
7. DO YOU HAVE HISTORY OF HYPERTENSION, HEART DISEASE: YES/NO
8. DO YOU CONSUME ANY DRUGS: YES/NO
9. IF YES, NATURE OF ILLNESS FOR WHICH DRUG IS CONSUMED:
10. DO YOU SMOKE CIGARETTES: YES/NO
11. IF YES:
    a. DURATION OF SMOKING:
    b. NUMBER OF CIGARETTES SMOKED PER DAY:

B.MASTER CHART (STUDY GROUP) – SDNN BEFORE AND AFTER QUITTING SMOKING.

SL.NO.	AGE	DURATION OF SMOKING (YRS)	NO. OF CIGARETTES PER DAY	PACK YEARS	SDNN BEFORE QUITTING(s)	SDNN AFTER QUITTING(s)
1	36	23	20	23	0.051	0.081
2	33	9	23	9	0.065	0.103
3	44	21	12	11	0.333	0.113
4	45	25	30	37	0.073	0.093
5	44	25	25	31	0.034	0.078
6	35	14	15	10	0.09	0.106
7	45	32	20	32	0.031	0.103
8	40	12	20	12	0.033	0.093
9	48	33	15	25	0.024	0.086
10	45	24	6	6	0.076	0.122
11	46	20	15	15	0.029	0.092
12	29	9	25	11	0.037	0.041
13	35	13	10	7	0.034	0.042
14	29	5	12	3	0.061	0.07
15	40	20	8	10	0.041	0.063
16	42	20	10	10	0.067	0.072
17	30	9	20	9	0.084	0.083
18	35	16	15	12	0.032	0.052
19	44	24	20	24	0.045	0.091
20	39	25	15	19	0.021	0.059
21	40	16	10	8	0.041	0.092
22	45	20	15	15	0.045	0.09
23	46	28	20	28	0.027	0.073
24	37	10	15	7.5	0.015	0.05
25	39	10	10	5	0.031	0.063
26	36	18	20	18	0.068	0.11
27	44	15	10	8	0.02	0.04
28	48	10	10	5	0.117	0.120
29	47	15	9	8	0.037	0.050
30	40	20	10	10	0.02	0.04
31	42	10	6	3	0.034	0.065
32	29	11	5	3	0.038	0.056
33	31	10	15	8	0.031	0.069
34	45	25	10	13	0.036	0.056
35	32	15	15	11	0.037	0.065

C.MASTER CHART (CONTROLS) : SDNN OF BASELINE AND 1 WEEK APART

Sl No.	AGE	SDNN(s)	SDNN(s) AFTER 1WEEK
1	47	0.068	0.076
2	49	0.079	0.080
3	29	0.076	0.071
4	43	0.076	0.076
5	39	0.09	0.080
6	49	0.063	0.070
7	49	0.097	0.087
8	44	0.056	0.060
9	47	0.075	0.084
10	40	0.054	0.066
11	30	0.047	0.050
12	29	0.256	0.197
13	30	0.071	0.085
14	28	0.091	0.085
15	43	0.089	0.094
16	34	0.078	0.070
17	28	0.082	0.086
18	49	0.07	0.074
19	27	0.084	0.088
20	45	0.067	0.072
21	40	0.068	0.070
22	32	0.078	0.072
23	34	0.07	0.068
24	38	0.086	0.080
25	18	0.07	0.068
26	18	0.085	0.084
27	18	0.096	0.094
28	40	0.071	0.076
29	36	0.084	0.083
30	43	0.078	0.065
31	38	0.087	0.074
32	35	0.078	0.076
33	40	0.068	0.064
34	37	0.078	0.074
35	34	0.085	0.083