Chapter 1

Importance of Heart Rate in Health and Disease

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Learning Objectives

At the end of this chapter one should be able to:

- Heart rate and its epidemiology
- Regulation of heart rate and significance of I_f channel
- Factors affecting HR and HRV
- Genetic influences on HR and longevity
- High RHV and its association with adverse clinical and cardiovascular outcomes

HEART RATE (HR) AND ITS EPIDEMIOLOGY

Resting heart rate (RHR) is one of the simplest accessible parameters and the most basic indication of life.[1,2] According to the American Heart Association (AHA), the ordinary sinus HR lies in the range of 60 and 100 beats per minute (bpm).[3] Usually, lower HR demonstrated lower all-cause and cardiovascular (CV) mortality.[1] In several studies, it has been shown that low RHR is connected with well-being and increased life span, and on the contrary, a high RHR is related to illness and unfavorable events.[4]

Historical Perspective of HR

HR evaluation has been a prognostic marker of health and disease for centuries. It has been used in a wide range of ancient societies and till now it is being utilized as a health indicator. In 3000–1600 BC, Egyptian papyri composed a portrayal of how to measure the pulse rate.[4] In 600 BC, Sage Kanada, an Indian doctor and logician expressed the assortment of heartbeats during various physiological and pathological conditions in his book, "Science of Sphygmica". In 500 BC, Ayurveda began in the Indian subcontinent, and since that time evaluation of the heartbeat is an indispensable part of Ayurvedic medicine.[5] In 129–200 AD, Greek doctor and Sphygmologist, Galen was well-known for his prophecy established on HR. According to Galen, the pulse has around 27 features which assume a significant role in determining well-being. However, he considered HR as the most significant feature.[4]

Demographic Determinants of HR

HR differs according to sex, age, weight/BMI, and rest. The normal grown-up male pulse is somewhere in the range of 70 and 72 bpm, while the normal for grown-up

women is somewhere in the range of 78 and 82 bpm. This distinction is mainly due to the size of the heart, which is ordinarily smaller in females than males. The smaller female heart, pumping less blood with each beat, needs to beat at a faster rate to match the larger male heart's output. Further, women have alternate intrinsic rhythmicity to the pacemaker of their hearts, which makes their heartbeat faster.[6]

As age progresses, there is an expansion in both septal and wall thickness in both genders; however, the left ventricular diameter increases only in males.[6] Autonomic influences on HR are also impacted by aging. With aging in man, decreased HR responses to β-adrenergic agonists and exercise are seen. A parasympathetically mediated respiratory change in pulse diminishes with maturing, and muscarinic parasympathetic blockade with atropine brings about lesser increments in HR in healthy elderly *vs* younger people. The beat-to-beat variation in HR is utilized as an indicator of cardiac autonomic reactions. From childhood to adulthood, a significant distinction in HR is seen. Many investigations have shown a decrease in regions of high-frequency peaks from ages 9 to 30 and diminished low-frequency peaks from childhood through middle-age.[7]

Devoted athletes are known to have slower HR than non-athletes. The heart, like a muscle, boosts its strength because of exercise training, especially with aerobic training. The HR in female athletes and regular exercisers will be lower than that of an amateurish untrained male; anyway, it will, in any case, beat at a quicker rate than a similarly skilled male athlete or regular exerciser.[6] It is likewise seen that overweight and obese individuals have a higher HR than individuals with normal weight, due to their higher metabolic rate and a lesser proportion of body surface to body weight, contrasted with individuals with ordinary weight. A strong connection between HR and wet bulb globe temperature (WBGT) has been further observed. As per an investigation directed to decide the impacts of work environment heat on laborers showed that, HR increases by 1 bpm when the ecological temperature increases by 1°C.[8]

There is a strong correlation between sleep and HR. During sleep, the routine physiological demands are reduced and temperature and blood pressure (BP) drop. One of the potential benefits of sleep is to allow the heart to rest from the steady requirements of wakefulness. As compared to awakening, during non-rapid eye movement (REM) sleep, the overall HR and BP are reduced. During REM sleep, however, there is a more pronounced change in CV activity, with overall increases in BP and HR.[9]

Photoplethysmography (PPG) allows quantifying real-world HR related to age, time, socioeconomic profile, comorbidities, and chronotropic medication use. In the Health eHeart Study, a total of 66,788 patients contributed 3,144,332 HR-PPG estimations between 1st April 2014 and 30th April 2018, leading to a formation of a "full HR-data set". From this data, information was collected relating to mean age, sex, BMI, and average steps per day, as estimated by their smartphone. Results showed that the real-world HR was 79.1 bpm ± 14.5. Females had a normal HR-PPG 4.4 bpm higher than men. As age increased, the 95% confidence interval (CI) of HR estimated by PPG values narrowed in women more than men. The 95th percentile of real-world HR was ≤110 in people aged 18–45, ≤100 in 45–60 age group and ≤95 bpm in those whose age was over 60 years. The 95th percentile of real-world HR was consistently under 100 bpm in people above 45 years old reaching approximately 95 bpm at 61 years old. Asian females revealed the most elevated HRPPG, which was 79.2 ± 14.3 bpm. The number

of medical ailments, female gender, increasing BMI, and being Hispanic were the factors related to an increased HR. Thus, it can be concluded from the result that age, height, and numbers of steps are negative indicators of pulse, while female gender, BMI, Asian race, and multi-nationality are indicators of a higher HR.[3]

Estimating a person's HR is a standard part of a clinical assessment, yet no action has been taken based on this finding unless it is well outside a population-based typical range. Quer G *et al.* during a period from March 2016 to Feb 2018, led a retrospective, longitudinal cohort study by including 92,457 people who wore a pulse wrist-worn tracker for a minimum of 20 hours/day. Individual daily RHR and its association with age, BMI, sex, sleep duration, and its variation over time were reported. The results revealed that the mean RHR for all people over the monitored days was 65.5 ± 7.7 bpm, with a minimum and maximum RHR for every individual extending somewhere in the range of 39.7 and 108.6 bpm, respectively. It was likewise observed that women had an essentially higher RHR in all age groups. Across age groups, normal RHR showed an increase until around 50 years and afterward started a descending pattern. RHR and BMI showed a U-shaped relationship. The most reduced RHR was related to a BMI of 21 for women and 23 for men. Normal day-to-day sleep length was additionally connected with RHR, with the minimum RHR registered for people who slept an average of 7–7.5 hours per night. Differences in RHR as a function of age, BMI, and sleep duration were all statistically significant (p <0.01).[10]

Likewise, sex alone was liable for 4% of the difference in the normal RHR among people, while sex and age together represented 6% of the fluctuation, sex and BMI for 7%, and sex and sleep duration for 5%. Sex, age, BMI, and sleep duration together were responsible for no more than 10% of total inter-individual variability.[10]

Take Home Pearls

- RHR is one of the easiest accessible parameters, and AHA defines the normal sinus HR as between 60 and 100 bpm.
- HR may vary with sex, age, weight/BMI, and sleep.
- Women generally have higher HR compared with men.
- Aging alters autonomic influences on HR regulation.
- Overweight and obese people have a higher HR than people with normal weight, because of their higher metabolic rate and a smaller ratio of body surface to body weight, compared to people with normal weight.

REGULATION OF HR AND SIGNIFICANCE OF I_f CHANNEL

Regulation of HR

HR is controlled by the sympathetic and parasympathetic processes of the autonomic nervous system (ANS) (Fig. 1.1). The parasympathetic system works under relaxed situations while the sympathetic system needs the energy to alert the body in an emergency or stressful condition, i.e. fight or flight state. The sympathetic nervous system (SNS) discharges norepinephrine (NE), enhances the HR and myocardial contractility, and is initiated during exercise, emotional excitement, or pathological conditions, for example, heart failure. The parasympathetic nervous system (PNS) discharges acetylcholine (ACh) and reduces HR.[11]

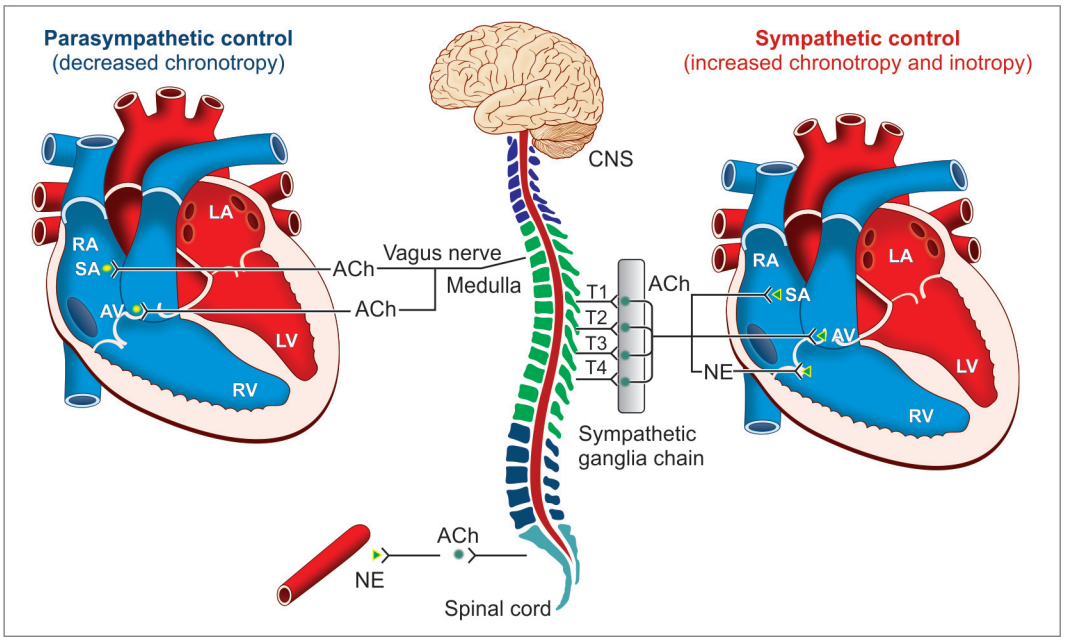

Fig. 1.1: ANS regulation of the heart function. The ANS affects the rate and force of heart contraction. CNS: Central nervous system; RA: Right atria; LA: Left atria; RV: Right ventricle; LV: Left ventricle; SA: Sinoatrial node; AV: Atrioventricular node; NE: Norepinephrine; ACh: Acetylcholine

Cardiac Conduction System

During the normal lifespan, the human heartbeats around 2.5 billion times, an accomplishment achieved by cells of the cardiovascular conduction system (CCS). The functional elements of the CCS can be extensively separated into the impulse-generating nodes (SA node and AV node) and the impulse-propagating His-Purkinje system.[12,13]

Cardiac Action Potential (CAP)

Electrical impulses are the results of the action potential, which is initiated by the sinoatrial (SA) node. This electrical impulse then goes through the heart's electrical conduction system to cause myocardial contraction. The SA node persistently creates electrical impulses, in this way setting the ordinary rhythm and rate in a healthy heart. In the SA node cells, numerous ion channels are present, which help to maintain the ions flow through the channels like sodium channel, HCN channel, calcium channel, and potassium channel.[14]

Channels from the SA Node and CAP Perspective

Hyperpolarization-activated Cyclic Nucleotide-gated (HCN) Channel

HCN channels are additionally called pacemaker channels because of their assumed impact on HR. It has a place with the superfamily of voltage-gated ion channels, and shows increased activation in response to the binding of cyclic adenosine monophosphate (cAMP) to a domain in the C-terminus called the Cyclic Nucleotide-

Binding Domain (CNBD).[15] The activities of the pacemaker start and sustain the electric activity of the heart, independent of the underlying innervations.[16]

Sodium Channel

The sodium channel is a voltage-gated ion channel that looks like an arch-type and consists of 4 homologous domains, arranged in a manner of 4-fold circular symmetry to form the channel. Each sodium channel opens quickly (<1 ms) during over 99% of depolarization. The sodium channel of the cardiac system has consent destinations for phosphorylation by Protein Kinase A (PKA), Protein Kinase C (PKC), and Ca-calmodulin kinase.[16]

Calcium Channel

Calcium channels regulate excitation-contraction coupling, emission, and the activity of many proteins and ion channels. They are the main gateway of the passage of calcium into the cells, a system of intracellular storage sites, and transporters such as the sodium-calcium exchanger. In cardiac muscle, two types of calcium channels are present in the SA node, L-type (low threshold type) and T-type (transient-type).[17] Both these calcium channels differ significantly in their electrical and chemical characteristics and also in the location of these channels in tissues. The L-type channel is responsible for typical myocardial contractility and vascular smooth muscle contractility, and it is commonly found in all cardiac cell types, whereas the T-type channel is found principally in a pacemaker, atrial, and Purkinje cells. It helps in regulating vascular tone, cardiac pacemaking, signal conduction, and also helps in the discharge of certain intercellular transmitters.[17]

Potassium (K^+) Channel

The cardiac K^+ channel is broadly categorized into three categories: Voltage-gated, internal rectifier channels, and the background K^+ currents. They are also highly regulated and are the basis for the change in action potential configuration in response to variation in HR.[18] Potassium conductance through the potassium channel during the moderate diastolic depolarization will expand the most extreme diastolic potential and moderate the pace of pacemaker depolarization prompting a slower HR.[17]

The Cardiac Rhythm: Ion Channels

The cardiovascular activity expected outcomes from the progression of ions through ion channels, which are the membrane-bound proteins that structure the basic machinery behind heart electrical edginess. Because of changes in electrical potential over the cell membrane, ion channels open and permit particles to go inside the cell and outside the cell along their electrochemical slopes.[19] Ca channel T-type, Ca channel L-type, *K* channel, I_f channel are the four primary diverts that are engaged with the electric impulse of SA node (Fig. 1.2).[15]

Phases of the Normal Action Potential

Phase 4 is the unconstrained depolarization (pacemaker potential) that triggers the action potential once the membrane potential arrives at a limit between –40 and –30 mV. At the point when the membrane likely is negative (about 60 mV), ion channels open that lead a low, inward (depolarizing) Na^+ current. These currents are classified as "funny" current and truncated as I_f. These depolarizing currents prompt the

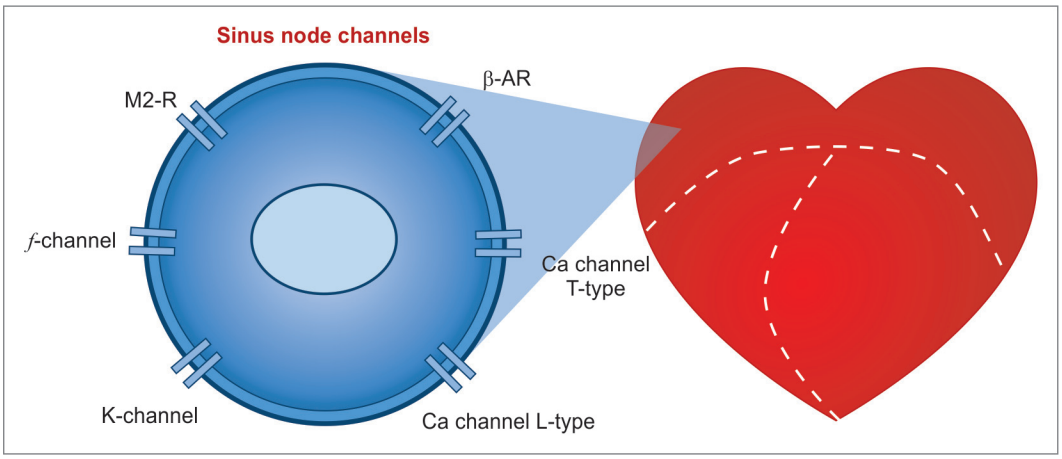

Fig. 1.2: Sinus node and its channel

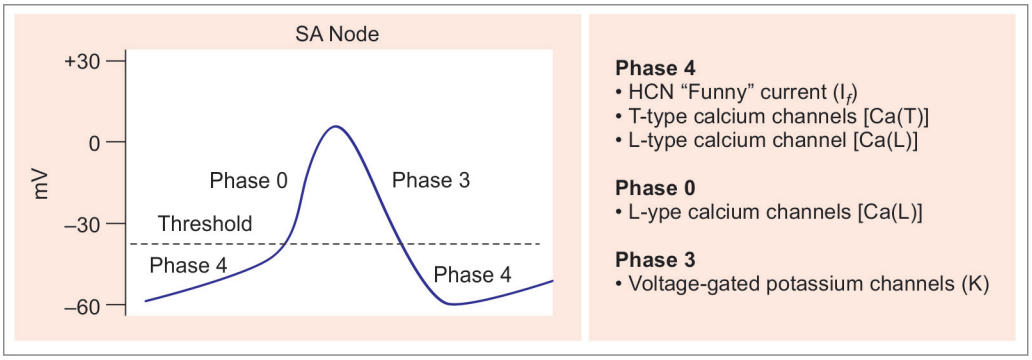

Fig. 1.3: Membrane potentials and ion movement in cardiac conductive cells

membrane potential to start and spontaneously depolarize and thereby starting Phase 4. As the membrane potential reaches about –50 mV, another kind of channel opens. This channel is called transient or T-type Ca^{++} channel. As Ca^{++} enters the cell through these channels down its electrochemical inclination, the inward-directed Ca^{++} flows further depolarize the cell. At the point when the membrane depolarizes to about –40 mV, the second kind of Ca^{++} channel opens. These are the so-called long-lasting or L-type Ca^{++} channels (Fig. 1.3). The opening of these channels causes more Ca^{++} to enter the cell and to additionally depolarize the cell until an activity potential limit is reached (normally between –40 and –30 mV).

Phase 0 depolarization is mainly caused by enhanced Ca^{++} conductance (gCa^{++}) via the L-type Ca^{++} channels that started to open at the end of Phase 4. The "funny" currents and Ca^{++} currents through the T-type Ca^{++} channels decline during this phase as their respective channels remain close. Since the movement of Ca^{++} through these channels into the cell is not quick, the pace of depolarization (slope of Phase 0) is much slower than found in other heart cells (e.g. Purkinje cells).

Phase 3 repolarization happens as K^+ channels open (increased gK^+) in this way increasing the outward-directed, hyperpolarizing K^+ flows. Simultaneously, the L-type Ca^{++} channel become inactivated and close, which decreases gCa^{++} and the inward depolarizing Ca^{++} currents.[20]

I_f Channels and their Significance in Regulation of HR

The pacemaker current, I_f, is vital in the initiation and control of HR. Its dynamic activity begins towards the finish of the repolarization. This channel is activated by intracellular cAMP.[21,22] I_f plays a significant function in the generation of pacemaker action and the regulation of HR. I_f is named 'funny' because of its two peculiar properties: (1) It is a blended sodium-potassium inward current actuated upon hyperpolarization (conversely with most voltage-gated flows), (2) it is directly regulated by cyclic nucleotides.[23]

The *f*-channels are comprised of the tetrameric relationship of protein subunits coded by the HCN gene channels, which convey the I_f are assigned as HCN channels.[21] HCN channels are actuated by hyperpolarization in the normal range of diastolic membrane potentials. The flows through HCN channels in the SA node are called I_f. It plays a significant key role in the generation of diastolic depolarization and redundant action, as it is enacted by hyperpolarization rather than depolarization.

HCN channel family has four members: HCN1–4, of which the most prevalent family member is HCN4, present in the SA node. cAMP enhances the probability of HCN channel opening (specifically of HCN4, the cardiac pacemaker isoform) and is therefore directly involved in *f*-channel gating (Fig. 1.4).[21]

The SA node of mammalians is innervated densely with autonomic nervous filaments, controlling heart chronotropic. Sympathetic β-adrenergic stimulation acts by increasing and parasympathetic muscarinic by slowing CV rate. When SA node cells are combined with solutions containing low concentrations of adrenergic agonists, acceleration of unconstrained rate is related to a more extreme slant of diastolic depolarization, with small alteration of action potential duration and shape.

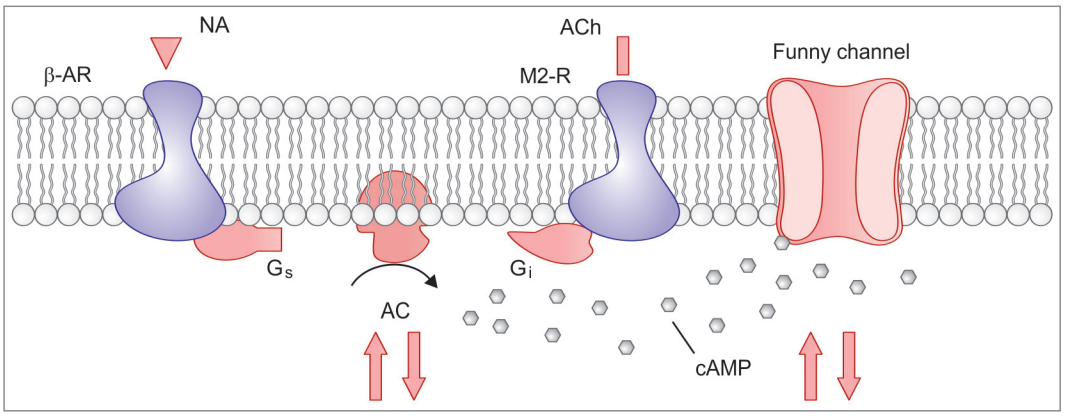

Fig. 1.4: SA node myocyte membrane showing modulation of native funny channels. **ACh:** Acetylcholine; **AC:** Adenylate cyclase; **β-AR:** β-adrenergic receptor; **G_i:** Inhibitory G-protein (inhibits AC); **G_s:** Stimulatory G-protein (stimulates AC); **M2-R:** Type-2 Muscarinic receptor; **NA:** Noradrenaline (norepinephrine); cAMP: Cyclic adenosine monophosphate

Several additional observations give a definite portrayal of I_f features and more evidence supporting its significance to pacemaker generation and rate control. It has been shown, for example, that β-AR incitement increments I_f by moving the actuation bend of the current to more positive voltages, without alteration of the conductance. The depolarizing shift of the I_f initiation curve is attributable to the β-AR-dependent increment of intracellular cAMP, the second messenger in I_f adjustment. As I_f is controlled by intracellular cAMP and is therefore initiated and repressed by β-AR and M2-R incitement. It represents an essential physiological mechanism intervening autonomic regulation of HR.[24]

I_f channels actuate the diastolic depolarization periods of the SA node activity potential and enhance the rate actuation caused by sympathetic incitement. It also mediates the cAMP-dependent modulation of HR by sympathetic (positive chronotropic, β-adrenergic) and parasympathetic (negative chronotropic, muscarinic cholinergic) stimuli (Table 1.1).[21]

Table 1.1: I_f mediates sympathetic and parasympathetic stimuli

Sympathetic stimuli	*Parasympathetic stimuli*
β-adrenoceptor stimulation	Muscarinic cholinoceptor stimulation
Activation of adenylate cyclase	Inhibition of adenylate cyclase
Increased local cAMP concentration	Decreased local cAMP concentration
Increased cAMP binding to HCN channels	Decreased cAMP binding to HCN channels
Increased likelihood of channel opening during diastole	Decreased likelihood of channel opening during diastole
Increased rate of diastolic depolarization	Decreased rate of diastolic depolarization
Increased heart rate	Decreased heart rate

cAMP: Cyclic adenosine monophosphate; **HCN:** Hyperpolarization-activated cyclic nucleotide-gated.

Heart Rate Variability (HRV)

HRV is the difference in time between the peaks of the heart in RR spans, which are the result of continuous interaction between two arms of the ANS.[25] Because of the impact of many factors, for example, mental or physical pressure, cardiovascular or non-cardiovascular disease, or pharmacological or invasive treatment, the heart fails to keep up to the same tempo from one heartbeat to the next. By enhancing or diminishing its tempo, the heart responds to any stimulus, so that the body can adjust to any changes. HRV can likewise be recognized in terms of amplitude: Powerless, ordinary, or high. A high HRV is a sign that the heart is healthy as it shows greater adaptability to respond to any pressure (physiological or environmental). On the contrary, decreased HRV can be a result of medical problems and can influence immune capacities, self-regulation, and mental abilities.[26]

Take Home Pearls

- HR is regulated by the sympathetic and parasympathetic input of the autonomic nervous system.

- The human heartbeats 2.5 billion times during a normal lifespan, a feat accomplished by cells of the CCS.
- The SA initiates an action potential that results in an electrical impulse and Ca channel T-type, Ca channel L type, K channel, and I_f channel are the four main channels involved in the electric impulse of the SA node.
- Out of all these channels, I_f plays a major role in the generation of pacemaker activity and the regulation of HR. It both initiates the diastolic depolarization phases of the SA node action potential and accelerates the rate initiation caused by sympathetic stimulation.
- The fluctuations in the time intervals between adjacent heartbeats are termed HRV.
- A high HRV is a sign that the heart is healthy since it has more flexibility to react to any stress, and on the other hand, a reduced HRV is a symptom of health problems and can affect immune functions, self-regulation, and psychological abilities.

FACTORS AFFECTING HR AND HRV

I. Physiological and Pathological Factors

Immune dysfunction leads to low HRV because of incompetent cholinergic reflexes using proinflammatory cytokines. In the long term, this leads to inflammation and cardiovascular disease (CVD). Pathophysiological factors that can affect the HRV are endocrine, respiratory, CV, and neurological factors.[26]

- **Endocrine factors:** Thyroid hormone influences the myocardium by increasing its contractility, but also on the ANS by modifying the sympathetic response. On another side, estrogen levels are connected with HRV measures in healthy women, hence affirming the cardio defensive impact of feminine sexual hormones. Masculine androgens have an advantageous impact (parasympathetic) on the heart autonomous modulation (higher HRV with high testosterone levels) while estradiol tends to incite a parasympathetic action.[26]
- **Neurological factors:** Heart and brain have numerous neural connections between them. If any single structure is impacted HRV will, likewise, be influenced. Neurological disorders associated with brain damage are linked with an HRV decrease: Parkinsonism, spinocerebellar degeneration, Shy-Drager syndrome, multiple sclerosis, Guillain-Barré syndrome. An increase in HRV might, in turn, beneficially affect the symptoms or the pace of the neurological disease.[26,27]
- **Respiratory factors:** Thoracic respiration greatly impacts HRV. A physiological phenomenon happens at every respiration: The respiratory sinus arrhythmia (RSA) where the heartbeat increases with inspiration and decreases with every expiration. Two mechanisms describe RSA: involving tonic and phasic chemo- and barometric reflexes, heart, and lung stretching reflexes, some local metabolic factors, central generators of heart rhythm, and the corresponding nerves (X particularly). RSA is also influenced by other factors, including age, gender, ethnicity, posture, and cardiopulmonary function. These variables can also, in turn, affect the HRV.[26,28]
- **CVD:** HRV is lower for subjects with high BP rather than for subjects with normal BP. A comparative relationship could be built up with an elevated level of blood cholesterol or glucose (diabetes) and a diminished HRV, in this way a reduced HRV can indicate the development of CVD.[26]

- **Other factors:** Many parameters influence HRV, for example, body temperature. If the temperature of the body diminishes enough, it can initiate bradycardia. Alternatively, when the temperature of the body increases as in fever, the heart rate accelerates. The change in HR with these parameters show that ANS and CNS are not by any means the only controllers of HRV; other physiological components are additionally involved.[26]

II. Lifestyle Factors

Lifestyle factors which can influence the HR variation are physical activity, alcohol, tobacco, and drug consumption and meditation, etc.[26]

- **Physical activity:** Physical activity, which can vary from one individual to another, is known to change HRV by diminishing sympathetic activation. According to the Whitehall study, HRV was found to be higher (and cardiac rhythm lower) in subjects having physical activity from moderate-to-vigorous levels. Also, supervised and non-supervised exercise therapy could increase HRV in patients affected by CVDs and diabetes mellitus.[26] Exercise training studies have shown a significant rise in HRV after significant improvements in aerobic capacity. Meersman found that routine aerobic exercise seems to play a role in the maintenance of increased HRV in active men when compared with age- and weight-matched in active individuals. This phenomenon suggests the beneficial role of long-term aerobic exercise in mitigating the age-dependent loss of HRV in physically active persons. There is evidence to suggest that low-pressure cardiopulmonary and high-pressure baroreceptor reflexes might be involved in this.[29]
- **Alcohol, tobacco, and drug consumption:** Utilization of tobacco and alcohol additionally affects HRV. Chronic smokers and alcohol consumers have low HRV; however, this impact is reversible when they quit drinking alcohol or smoking. Alcohol incites an HRV decrease by sympathetic activation or a parasympathetic inhibition.[26] Both active and passive smoking leads to an increase in HRV. Regular consumption of excessive alcohol reduces HRV; while moderate alcohol consumption does not change the HRV drugs can likewise impact HRV. A few drugs (e.g. β-blockers, ACE inhibitors, and psychotropic drugs) have been found to have a direct or indirect influence on HRV.[30] Tricyclic antidepressant medication significantly decreased HRV. Furthermore, results from a study conducted by Dikariyanto *et al*. reveal that snacking on whole almonds instead of typical snacks may reduce the risk of CVD partly by ameliorating the suppression of HRV during periods of mental stress.[31]
- **Meditation:** HRV can be utilized as an indicator of a meditative state. In a transversal study, it was discovered that autogenic meditation (also called "Schultz's autogenic training") prompts an increase of cardiac coherence (CC) score, and of alpha, beta, and gamma brainwaves, and it indicates an improved structural or functional connection between cortical and thalamic regions. This increase is related to an increased attention span and reinforced autonomous regulation (ANS).[26]

III. Non-modifiable Factors

- **Age:** Although RHR is not directly related to increasing age, there is a reduction in HRV as age progresses, which might be a biological marker of the aging process. The impact of aging on HRV has been attributed to a decrease in efferent vagal

cardiac tone and diminished β-adrenergic responsiveness. Autonomic derailments can be responsible for increasing cardiovascular degeneration in the aging population, moving the autonomic balance toward sympathetic dominance.[29]

- **Gender and ethnicity:** It has been known that there is a distinction among people in the way the ANS is controlled and thus in the sympathetic–parasympathetic balance and this shows itself in varying HRVs. This contrast between the sexes diminishes as individual approach the age of 50, a fact that is ascribed to the postmenopausal hormonal changes that occur in women.

  In the systemic review, Thayer *et al*. mentioned that ethnicity affects BP and subsequently on HRV. The ethnic origin appears affect HRV. In a meta-analysis including 17 studies and a sum of 11,162 test subjects, Hill *et al*. established a fundamentally higher short-term resting HRV in the Afro-American people than in American people of European origin.[26,30]

IV. Environmental Factors

Apart from environmental conditions and profession related influences, some harmful substances can also affect HRV.[30] These factors include environmental particulate matter, several chemical components, electromagnetic fields (EMF), vibrating tools, psychosocial charge, working time, fatigue, etc. Long-term exposure to these factors causes a decline in HRV.[26] Environmental factors prompt changes in HRV due to the physiological reaction of the vegetative sensory system. SNS activity is increased by heat, which reduces HRV. However, long-term exposure to cold (e.g. at work or throughout winter) has not been found to affect HRV because of adaptation effects. Exposure to the commotion, induced pain decreases HRV due to its impact on SNS activity. Night shift works over numerous years have a lower HRV due to the chronodisruption.[30]

V. Neuropsychological Factors

HRV is not linked to the only personality but a list of psychological considerations, for example, stress, depression, and negative emotions.[26]

- **Stress:** Stress is a very important factor that impacts HRV. Many stressful conditions can lead to low HRV, for example, anxiety, hostility, depression, and work stress. Many analyzed studies uncovered a noteworthy connection between a significant level of work pressure and low HRV. Stress also corresponds with a greater risk of CVD and a high HR.[26]
- **Depression:** The low HRV value, even if depression is not correlated with a CVD, remains an indicator of poor health. A meta-analysis by Kemp showed a significant correlation between depression and a low HRV.[31]
- **Negative emotions:** Many negative emotions like outrage, tension, dissatisfaction, and worry can lead to a diminished HRV.[26] A transversal study on healthy subjects affirmed the significant correspondence between weak neuroticism (negative emotions) and diminished HRV and the inverse as well. Kemp and Quintana also concluded that HRV holds significant functional importance on social conduct, self-regulation, and mental adaptability against life stressors.[32]

Measuring HR and HRV

Monitoring and analysis of HR give important data concerning well-being status and have been widely researched in various activities of healthy subjects as well as in

patients experiencing different diseases.[33] To limit the impacts of various confounding factors, the estimation of HR ought to be carefully standardized.[34] According to the Consensus Panel of the European Society of Hypertension, the accompanying data ought to be given in considers detailing HR information: (1) Resting period before estimation; (2) ecological conditions; (3) strategy for estimation; (4) number of estimations; (5) span of measurement; (6) body position; and (7) nature of the observer. The following are the suggestions given by the board concerning how HR ought to be measured.[35]

Procedures for HR Measurement[35]

- The patient ought to be permitted to sit for at least 5 minutes in a quiet room at an agreeable temperature.
- HR ought to be estimated over a 30-second time frame by pulse palpation.
- At least two estimations in the sitting position ought to be taken.
- For subjects in whom orthostatic BP estimation is performed, HR ought to be estimated after each BP perusing.
- Results may differ as per whether HR is estimated by a specialist, a medical caretaker, or a programmed gadget.
- Patients performing self-BP estimation should likewise gather HR information.

Techniques for HR Measurement

Traditionally, HR is estimated by pulse palpation.[34] Apart from pulse palpation, different techniques to quantify HR incorporate ECG-and PPG-based wearable gadgets. A brief overview of various HR measuring techniques and their principles are given below:

Pulse palpation: The pulse rate is estimated by including the beats in a set timeframe (from 15 to 60 seconds) and multiplying that number to get the number of bpm. The pulse rate can be estimated anytime on the body where an artery is near the surface.[34] The two most regular spots to gauge HR utilizing a two-finger palpation strategy are at the wrist (using radial artery) and the neck (through the carotid artery).[36]

Electrocardiography (ECG): With the help of ECG, HR is measured more accurately and for longer periods.[34] Dynamic ECG screens show HR, yet it can likewise be determined from a printed following utilizing both of two strategies:

- When the HR is standard, count the number of large (0.2 second) boxes between 2 progressive QRS and divide 300 by this number. The number of large time boxes is divided into 300 because 300 × 0.20 = 60, and HR are determined in bpm or 60 seconds. For instance, if there are 3 large boxes between QRS complexes, the HR is 100 bpm because 300 ÷ 3 = 100. Also, if 4 large time boxes are tallied between QRS complexes, the HR is 75 bpm (Fig. 1.5).
- If the HR is unpredictable, the principal strategy would not be precise because the stretches between QRS complexes differ from beat to beat. In most cases, the ECG chart paper is scored with marks at 3-second spans. In such cases, simply tally the number of QRS complexes every 3 or 6 seconds and multiply this number by 20 or 10, respectively.[37]

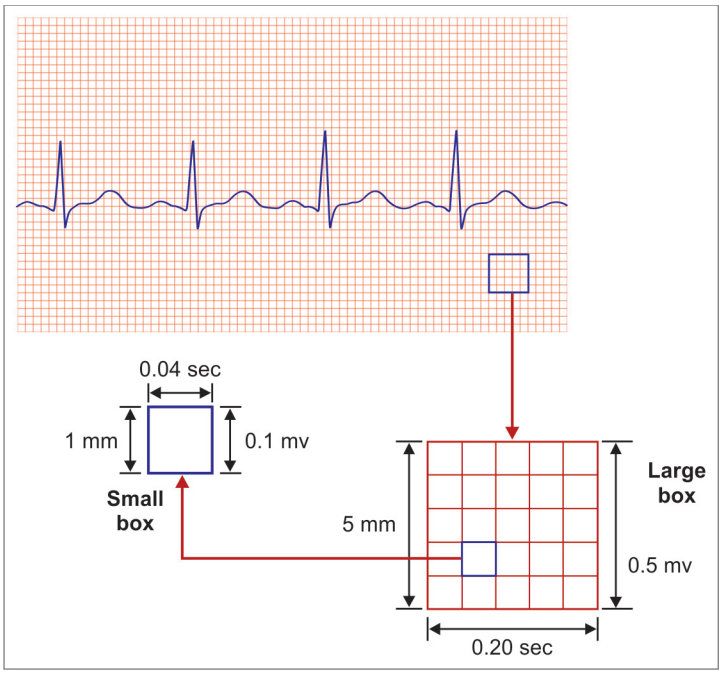

Fig. 1.5: The normal ECG tracing

- **Advantages:**[38]
  - High processing speed
  - Good reproducibility
- **Disadvantages:** An ordinary ECG is perpetually undermined by: [39]
  - Electrical impedance from encompassing hardware (for example, impacts of the electrical mains supply)
  - Measurement (or electrode contact) commotion
  - Electromyogram commotion (muscle contraction)
  - Movement heirloom
  - Instrumentation clamor (for example, an heirloom from the analog-to-digital conversion process).

Wearable devices and PPG: In the past few year's consumer wearable gadgets, include smartwatches, wristbands, wearable mobile sensors, and fitness trackers, have become exceptionally popular.[40] The ascent in the accessibility of consumer wearable devices that create well-being data gives an uncommon chance to change medical services by scientists, clinicians, and customers. These wearable gadgets depend on PPG, which is an optical method that identifies blood volume changes in the microvascular bed of tissue under the skin surface. PPG uses four segments to quantify HR: Optical producer, digital signal processor (DSP), accelerometer, and calculations (Fig. 1.6).[41,42] Wearable PPG sensors can utilize various shades of light, for example, green or red, to record these adjustments in blood volume to each having different expenses and benefits.[40]

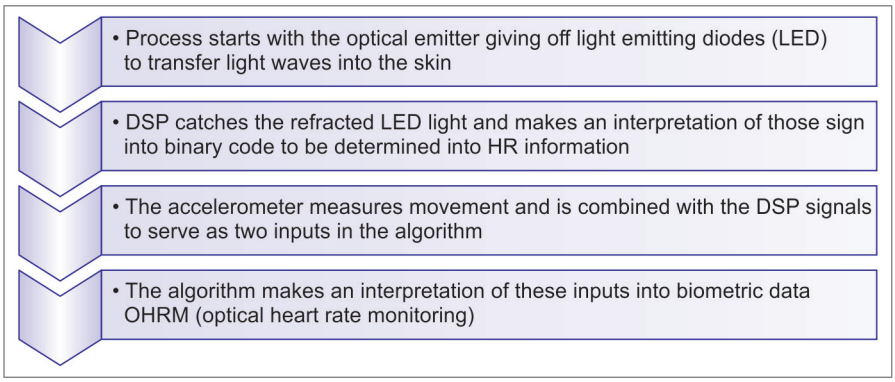

Fig. 1.6: PPG components to measure HR

- **Advantages:**[43]
  - Non-intrusive
  - Inexpensive
  - Convenient
- **Disadvantages:** Results of PPG may differ due to: [42,44]
  - Optical commotion (a portion of the light produced, which signs as bloodstream)
  - Skin tone (more obscure skin tones and skin with tattoos)
  - Crossover issue (blunder by the algorithm mistaking other inputs as HR data because of similar continuous movement)
  - Sensor area
  - Low profusion to limits can pose challenges dependent on low bloodstream and high optical commotion.
  - Tissue modification produced by voluntary or involuntary movements can make changes of inner tissues, for example, muscle movement and dilation of tissues.

Measurement of HRV

HRV, which represents the variation of the beat-to-beat interval, is a simple and non-intrusive technique to assess ANS functions that impact CV systems.[45] Three methodologies used to screen HRV: time-domain and frequency-domain measures are linear; whereas complexity measures offer a non-linear approach.[46] Clinicians and researchers measure HRV using time-domain, frequency-domain, and non-linear indices.[47]

- **Time-domain measures:** Time-domain indices quantify the amount of HRV observed during monitoring periods that may range from <1 minute to >24 hours. The statistical metrics include the SDNN, SDANN, SDNN Index, RMSSD, SDSD, NN50, pNN50, etc.[47] Out of all these time-domain measures, the SDNN, SDANN, and SDNNi indices are obtained long-term records and represent the sympathetic and parasympathetic activity, while the rMSSD and pNN50 indexes represent the parasympathetic activity, as they are found from the analysis of adjoining RR intervals.[48] Time-domain geometric methods allow the presentation of cardiac pulse intervals (systole and diastole) and use approximations to derive the HRV measurements. The main geometric methods used are triangular index (RRtri), triangular interpolation of RR intervals (TINN), differential index, and logarithmic index.[49]

- **Frequency domain (spectral estimation of the HRV):** Frequency domain estimations gauge the distribution of absolute or relative power into four frequency bands that include ultra-low-frequency (ULF), very-low-frequency (VLF), low-frequency (LF), and high-frequency (HF).[47,50]
- **Non-linear methods:** Non-linear indices measure the unpredictability and complexity of a series of interbeat intervals (IBIs).[48] The time arrangement 1, 2, 3, 1, 2, 3 has a similar inconstancy as the time arrangement 1, 1, 2, 2, 3, 3 and 3, 1, 2, 2, 3, 1, yet different underlying patterns. The non-linear analysis enables the measurement of this additional data. Essentially, the non-linear approach methodology measures the complexity of the signal; how frequently do similar patterns reoccur? [46]

Principle Disease Linked to HRV

CVDs are one of the fundamental causes of morbidity and mortality around the world. In developing countries, CVDs are responsible for approximately 17 million deaths every year. Cardiac autonomic dysfunction is a risk factor for the progression of CVD that can be measured non-invasively using HRV. HRV has relation to a wide spectrum of ailments (Fig. 1.7). Physiologically, HRV is the result of adaptive changes in HR caused by the sympathetic nervous system (SNS) and parasympathetic nervous

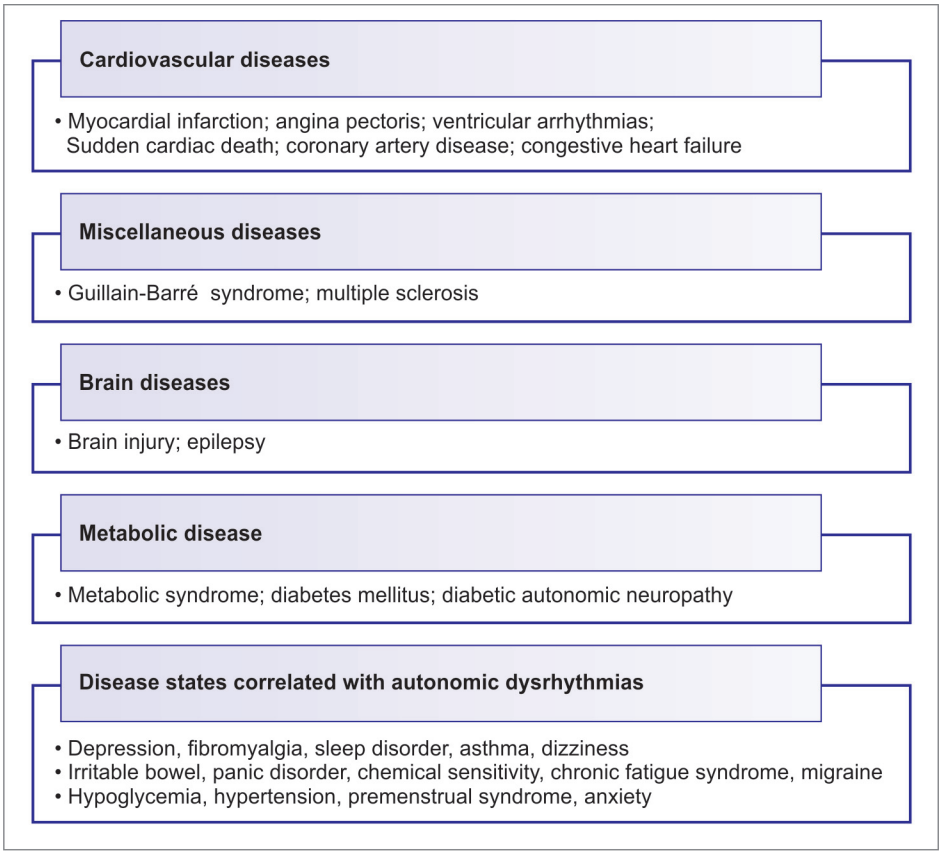

Fig. 1.7: Principal diseases related to HRV

system (PNS) with the purpose to buffer blood pressure (BP). Low HRV indicates a diminished adaptive capacity of ANS and is believed to increase morbidity. HRV has long been known to be related to morbidity and mortality after myocardial infarction (MI). Other than acute MI and cardiac death, events of congestive HF and arrhythmias have likewise been related to decreased HRV.[51,52]

When RHR should Consider Elevated?

Similar to the continuous discussion of a suitable cut-off for deciding hypertension (HTN), the limit of what ought to be viewed as an elevated HR is a discussion between the advantages and disadvantages of treatment. About 25% of the general population shows RHR above 80 bpm.[53]

In the National Health and Nutrition Examination Survey (NHANES), an RHR over 90 bpm was present in 5.2% of men and 8.4% of women. Whereas in the Cooper Clinic study, an RHR of >80 bpm was found to have a similar risk as a BP ≥140/90 mmHg. This could be utilized as a current reasonable guide. A threshold of >80 bpm ought no longer to be taken as an indication of sickness; however, a practical rule of thumb for urging people to improve the lifestyle factors identified with elevated RHR. These factors could include known CV risk factors, for example, decreasing smoking, increasing physical activity level, assessment of BP, lipids, and diabetes, and decreasing alcohol consumption and diet.[53]

Take Home Pearls

- Several factors may influence the HR and HRV (such as physiological and pathological factors, lifestyle, ecological, and neuropsychological factors).
- Monitoring and investigation of HR provide valuable information regarding health status in patients suffering from various diseases.
- HR can be measured with the help of the ECG technique, pulse rate method, PPG method, or by using health bands.
- Decreased HRV is an indicator of mortality and arrhythmic complications that is independent of other recognized risk factors.
- Cardiac autonomic dysfunction is a risk factor for the progression of CVD that can be estimated non-invasively using HRV.

GENETIC INFLUENCES ON HR AND LONGEVITY

RHR is inversely related to the average life span in most organisms. Indeed, among well-evolved creatures, where the relationship has been most intensively surveyed, there is a linear, inverse semilogarithmic relationship between average RHR and average life expectancy in all species. The association between HR and life expectancy has been attributed to the metabolic rate, which is more prominent in tiny creatures and is directly related to HR. There is a linear relation between RHR and longevity across different species. This relation, apart from humans, spans a 35-fold difference in heart rate and a 20-fold difference in the life span of other mammals. Numerous other factors influence HR, for example, genetic influences on the cell biology of electrically active atrial tissues, autonomic nervous activity, inflammatory processes, etc. Each of these factors that influence HR may likewise independently affect life expectancy.[54,55]

The average number of heartbeats per life is almost constant across species and is in the order of 10^9. Drawing from a wide allometric scale of 10^{20}-fold among living creatures, Azbel concludes that the energy utilization/body atom per HR is the equivalent in all creatures. According to his calculation, basal O_2 utilization is ~10 O_2 molecules/lifetime and in those creatures with a heart ~10^{-8} O_2 molecules/heartbeat. HR is essentially hypothesized as an epiphenomenon of the rate of basal O_2 consumption and heartbeat.[55]

According to twin studies in youth- and middle-aged grown-ups, the assessments of heritability, i.e. genetic variability expressed as a portion of the total variation in HRV, ranged from 13 to 65%.[56] Whereas another twin study of time-domain HRV measures, based on 24-hour ambulatory recordings yielded noteworthy heritabilities of time-domain variables ranging from 46 to 57% and demonstrated a considerable overlap of hereditary effects on two time-domain HRV measures: Standard deviation of the R-R intervals (SDNN) and the square root of the mean squared differences between successive R-R intervals (RMSSD).[57]

Genetic Determinants of HR

RHR reflecting the balance of sympathetic and parasympathetic inputs is genetically regulated in hierarchical and yet integrative biological networks, including the autonomous nervous and hormonal frameworks. In the observational investigations, RHR was recommended to be a modifiable factor or an important treatment target for individuals with CVD. Recent observations found a positive relationship between high RHR and the risk of impaired fasting glucose, metabolic syndrome (MetS), and type-2 diabetes (T2D). Studies showed a 1.89-fold risk in developing T2D and a greater than the 4-fold risk for MetS when comparing participants in the highest quintile of RHR with those in the lowest. Guo *et al*. conducted a genome-wide association study (GWAS) to understand the genetic relationship between RHR and cardiometabolic disorders/T2D. This study analyzed the genetic relationship, causality, and shared genetic qualities among RHR and T2D utilizing low-density (LD) score regression, summed up summary data-based Mendelian randomization, and transcriptome-wide association scan (TWAS) and summary level data for T2D and 8 cardiometabolic traits. Result revealed a significant hereditary relationship between RHR and T2D (r_g = 0.22; 95% CI: 0.18 to 0.26; $p = 1.99 \times 10^{-22}$), and 6 cardiometabolic traits (r_g range-0.12 to 0.24; all p <0.05). RHR has a significant assessed causal impact on T2D (odds ratio: 1.12 per 10 bpm increment; $p = 7.79 \times 10^{-11}$) and weaker causal impact from T2D to RHR (0.32 bpm per doubling increment in T2D prevalence; $p = 6.14 \times 10^{-54}$). These outcomes give insights into the shared etiology for high RHR and T2D.[58]

To gain more comprehensive insights into the genetic regulation of HR, den Hoed *et al*. in 2012, performed a 2 stage meta-analysis of GWAS in data from up to 181,171 individuals. In this meta-analysis, loci associated with HR were subsequently tested for association among HR and CVD and mortality. Also, experimental studies from *Drosophila melanogaster* and *Danio rerio* models as an initial step toward recognizing the causal genes within the associated loci were included to support the meta-analysis. Den Hoed identified that 14 new loci previously unknown, to be robustly associated with HR and affirmed the relationship with all 7 previously established loci. Also, results from experiments in *Drosophila melanogaster* and *Danio rerio* models support a role in HR regulation for 20 candidate genes from 11 loci that are applicable for HR regulation, and highlight a role for genes involved in signal transmission, embryonic

cardiac development, and the pathophysiology of dilated cardiomyopathy, congenital HF and/or sudden cardiac death. Also, genetic susceptibility to increased HR is related to alter cardiac conduction and diminished risk of sick sinus syndrome, and both HR- increasing and HR-decreasing variants associate with the risk of CVD. These observations provide new insights into the mechanisms that regulate or modulate HR in health and disease and provide a new perspective on the well-recognized association of HR with CVD and mortality.[59]

In several epidemiological studies, it was noticed that South Asian (SA) men and women worldwide have a high risk of CVD. Individuals of SA origin experiences a 1.5-fold increased coronary disease in contrast to the general population. SA individuals also have an increased prevalence of impaired glucose tolerance, insulin resistance, and T2D. Diabetes and dysglycemia are related to increased HR and abnormal cardiac sympathovagal balance and are indicative of increased coronary mortality. Bathula *et al*. in the study showed that on average, SA have 5 bpm higher HR-PPG than Europeans, observations that appeared to be genetically determined and were not linked with other risk factors.[60] Similarly, Neil *et al*. conducted a prospective cohort study, involving 200 SA and 200 caucasian healthy volunteers. P-wave indices, HRV, and anthropometry in SA volunteers were compared with white European healthy volunteers. SA were found to be of smaller height with lower lean body weight and smaller left atrial size. They had a higher mean HR and SA males had lower HRV, suggestive of sympathetic predominance.[61]

HR in the Indian Population

Indian population shows elevated RHR because of their increased sympathetic overactivity (SO). It relates to both systolic blood pressure (SBP) and diastolic blood pressure (DBP) as well as with BMI.[62] SO plays a significant role in the development of CVDs. It causes an elevation in HR, cardiac output, peripheral vascular resistance, and sodium reabsorption in the kidney and a consequent increase in BP. It is additionally found to be related to the prolongation of cardiac repolarization time and may plays a crucial role in increasing CVD in patients.[63] SO depends on the hormonal factors involved in the homeostatic control of the CV functions. According to a pan India, non-interventional, cross-sectional study, a noteworthy correlation has been found between SO and HR and also between SO and HTN.[63,64]

According to India Heart Study (IHS), the predominance of white coat hypertension (WCH) and masked hypertension (MH) in India is higher in comparison with worldwide data that is associated with increasing HR. In the Indian population, it was observed that the evening BP was higher than the morning SBP (127.8 ± 14.7 *vs* 129.8 ± 15.3) mmHG and DBP (81.9 ± 10.1 *vs* 82.4 ± 10.2) mmHg. The predominance of WCH was 24%, and 18% of the participants had masked HTN. More than half of the participants of IHS had an elevated RHR (79.8 ± 9.6 bpm). An elevated HR was more common in WCH.[65]

Another India Ambulatory Blood Pressure Measurement (ABPM) study was conducted between Jan 2017 to Nov 2018 to investigate sex-related differences in HR and BP patterns in 14,977 Indian subjects. The study revealed that women had higher HR both during the day and nighttime and they had a lower HR dip than men, suggesting a higher risk of all-cause mortality and CV events. During the daytime, females HR compared to men was (80.3 ± 11.2 *vs* 79.4 ± 11.5 bpm), at nighttime (71.4 ± 10.6 *vs* 68.9 ± 10.6 bpm), and over 24 hours (77.4 ± 10.6 *vs* 75.9 ± 10.6 bpm), respectively

(p <.001). For SBP, a lower daytime ABPM (131 ± 16 *vs* 133 ± 14 mmHg, p <.001) but higher nighttime ABPM (122 ± 18 *vs* 121 ± 16 mmHg, p <.001) was found in females compared to males. At nighttime in the ABPM study, it was observed that HR diminished when contrasted with daytime for both males and females, but this decrease at nighttime was larger for males than for females (–10.5 ± 8.0 *vs* –8.8 ± 6.8 bpm, p <0.001). Females, especially after menopause, had significant differences in ABPM limits when contrasted with males, thus indicating a less favorable CV prognosis.[66] According to the Beat survey, a cross-sectional study across India, comprising 3,743 patients with mean age 45.69 ± 6.86 years, Indian HTN patients display elevated RHR. The average RHR and BP in the Beat survey were discovered to be 82.79 ± 10.41 bpm and 146.82 ± 15.46/89.08 ± 8.8 mmHg. In this investigation, the HR was found to have relation with SBP (r = 0.247, p <0.01), DBP (r = 0.219, p <0.01); to lower extent with BMI (r = 0.041, p <0.05); yet not with age (r = 0.012, NS).[62]

Rajalakshmi *et al*. in 2012 led a cross-sectional study, to assess HRV in obese Indian young adults (n = 150) and to build up a relationship between HRV indices and obesity indices. The results of the investigation revealed that a significant increase in the mean HR, LF (nu), and LF/HF ratio was observed in obese people compared with the normal-weight group, whereas time-domain matrices variables, total power, HF(AV), and HF (nu) were altogether lower (p <0.05). Pearson's correlation coefficient demonstrated that time-domain matrices variables negatively correspond with BMI and waist stature ratio (WSR) which was statistically significant. Furthermore, on regression analysis, BMI was found to be a major predictor for HRV variations. The study results showed reduced HRV, higher sympathetic, and lower parasympathetic nerve movement in obese subjects. HRV indices were essentially related to obesity indices, and BMI is the significant determinant for the progressions in both time and frequency domain indices.[67]

Take Home Pearls

- A linear, inverse semilogarithmic relationship is observed between RHR and average life expectancy in all species aside from humans.
- The average number of heartbeats per life is almost steady across species and is in the order of 10^9.
- RHR has been suggested to be a modifiable factor or a significant treatment target for people with CVD.
- SA men and women have a high risk of CHD. They experience a 1.5-fold increased coronary disease risk compared to the general population.
- RHR has a wide variation across the world. Asians and Indians have been found to have a higher RHR.
- Indian population shows increased RHR because of their increased SO.

HIGH RHR AND ITS ASSOCIATION WITH ADVERSE CLINICAL AND CV OUTCOMES

Impact of High RHR in General Population without CVD

High RHR is a risk factor for CV morbidity and mortality in normal individuals as well as in patients with cardiac disorders. Among hypertensive individuals, raised HR is a common feature.[68] The heightened sympathetic tone has a crucial role in the connection between RHR and BP on the grounds that it causes an elevation in HR,

cardiac output, peripheral vascular resistance, and kidney sodium reabsorption, which thus leads to the rise of BP. High RHR is related to endothelial dysfunction, diminished artery compliance and distensibility, and thus increased arterial wall stress and raised pulsed-wave velocity, which is additionally connected with increased afterload and eventually systemic HTN.[69] Several investigations have exhibited that individuals with high HR have elevated BP readings and that this affiliation is stronger in subjects with raised sympathetic activity. The reasons may be that HTN and tachycardia having a mutual underlying factor: Increased sympathetic tone. In the Syst-Eur study (systolic hypertension in Europe); performed in elderly patients with systolic HTN, it was discovered that the patients with an HR >79 bpm had an 89% more risk of mortality than those with an HR ≤79 bpm.[70] Whereas in the Tensiopulse study, which assessed 38,145 patients, treated by 2000 general experts all over Italy, it was discovered that 30% of the hypertensive patients had an RHR ≥80 bpm.[68] On the other hand, data derived from Hypertension and Ambulatory Recording VEnetia Study (HARVEST) exhibited that baseline RHR and changes in HR in the first few months of follow-up were able to predict the development of sustained HTN in white, younger subjects assessed for stage 1 HTN.[69] The Kaliuan study furthermore indicated that around 40% of individuals without arterial HTN or cardiac arrhythmias at baseline developed HTN during the mean follow-up time of 3.5 ± 0.9 years. An increase in RHR by 10 bpm was associated with an 8% increase in new-onset of HTN.[71]

A rise in RHR is not just associated with a poorer outcome in patients with HTN but also in CAD. Among men and women without known CVD, an elevation in RHR over 10-year period was related to an elevated risk of death from IHD in patients with no known reason for mortality. Patients with RHR under 70 bpm at the first measurement yet more than 85 bpm at the subsequent assessment had a risk of death from IHD that was 90% higher, and risk of death from all causes that was 50% higher. Nauman J *et al*. utilized RHR as a constant variable and consolidated the squared estimation of RHR to assess nonlinear patterns. To allow visual assessment of the pattern, they presented hazard ratios for the following categories of change in RHR: (1) A decline of greater than 25 bpm; (2) a decline between 15 and 25 bpm; (3) a decline between 5 and 15 bpm; (4) a change from –5 to 5 bpm (reference); (5) an increment between 5 and 15 bpm; (6) an increment between 15 and 25 bpm; and (7) an increment of greater than 25 bpm.[72]

According to a British Regional Heart Study, during a follow-up period involving 7,735 individuals, in men with no confirmation of IHD, there was a substantial positive relationship between RHR and age-adjusted rates of all major IHD events (fatal and nonfatal), IHD-related deaths, and sudden cardiac death. After adjustment for age, SBP, cholesterol, smoking, social class, hefty drinking, and physical activity, this association was still noteworthy, though in men with prior IHD, the association was significant but less pronounced. It was observed that elevated HR ≥90 bpm is a risk factor, especially for sudden cardiac death; it is free of other built up coronary risk factors and is most obviously found in men with no past IHD at the time of the underlying examination. These findings from the study reveal that increased HR ≥90 is a risk factor for fatal IHD, especially for sudden CV death.[73]

As RHR is a non-invasive marker of cardiac function and a nice indicator of physical wellness and general well-being, raised RHR assessed at a single point is related to a higher risk of death from most causes, including cancer, independent of BP, and one of the main socio-demographic and lifestyle risk factor. According to the MCCS

accomplice study, a long-term increase in RHR was related to higher mortality. It was discovered in the study that all-cause mortality risk for participants whose RHR increased from <70 bpm to 70–85 bpm was higher by 24% compared with those who kept a healthy RHR of 70 bpm or less between the benchmark and wave 2. RHR monitoring during general practitioner visits or utilizing wellness gadgets could help distinguish population subgroups at higher mortality risk.[74]

Also, it was known that the degree of relationship between RHR and the risk of all-cause and CV mortality differ across investigations. Zhang D *et al*. in 2017 conducted a meta-analysis to quantitatively assess the relationship in the general population. An aggregate of 46 investigations were included in the meta-analysis, involving 1,246,203 patients and 78,349 deaths for all-cause mortality, and 8, 48,320 patients and 25,800 deaths for CV mortality. The relative risk with 10 bpm increase of RHR was found to be 1.09 (95% CI: 1.067–1.12) for all-cause mortality and 1.08 (95% CI: 1.06–1.10) for CV mortality. Patients with an RHR of 60–80 bpm had a relative risk of 1.12 (95% CI: 1.07–1.17) for all-cause mortality and 1.08 (95% CI: 0.99–1.17) for CV mortality, and those with an RHR of more noteworthy than 80 bpm had a relative risk of 1.45 (95% CI: 1.34–1.57) for all-cause mortality and 1.33 (95% CI: 1.19–1.47) for CV mortality. When contrasted with 45 bpm, the risk of all-cause mortality increased altogether with elevated RHR in a linear relation**,** yet an essentially increased risk of CV mortality was seen at 90 bpm. These findings revealed that higher RHR was independently associated with increased risks of all-cause and CV mortality.[75]

As there is a substantial connection between raised RHR and increased incidence of CVDs, elevated RHR somewhere in the range of 50 and 60 years old was found to be connected with an increased risk of CVD when contrasted with individuals with stable RHR. Chen XJ *et al*. in a 25-year follow-up study, revealed that men with an RHR >75 bpm at 50 years old have twice as high-risk of all-cause death, CVD, and CHD compared with men with RHR ≤55. As per their study, participants with a baseline RHR of >75 bpm in 1993 had about a two-fold higher risk of all-cause death compared with those with <55 bpm in 1993.[76]

Impact of High RHR in Patients with CVD

High RHR adds to CVD mortality by triggering the deposition of atherosclerotic plaques by exerting mechanical stress on the walls of the arteries. Raised RHR might point to underlying arrhythmias, which increment mortality risk.[74] In patients with CAD high RHR incites CV events primarily through ventricular arrhythmias or progressive pump failure. Additionally, coronary plaque disruption is likewise related to the elevated RHR, as it represents a predictor for coronary plaque instability. Studies have demonstrated that elevated RHR was related to higher triglyceride, total cholesterol, non-HDL cholesterol, and apolipoprotein B, as well as endothelial dysfunction which could be an additional factor that associates elevated RHR and CAD. The Kailuan study demonstrated that the risk of MI was 10% higher in the most noteworthy quintile bunch contrasted and the least quintile RHR gathering (HR: 1.10; 95% CI: 1.01–1.20). Whereas Aune *et al*. in the huge meta-analysis, including 12,27,511 participants revealed that a rise of RHR above 10 bpm was related to 7% higher risk of CAD (HR 1.07; 95% CI: 1.05–1.10) and 9% for sudden cardiac death (HR: 1.09; 95% CI: 1.00–1.18).[69]

Aging of the population, worsening risk factor profile, and improved management of acute CVD have all led to increased prevalence of heart failure (HF). RHR is

independently connected with outcome among patients with HF and RHR lowering has been exhibited to benefit patients with HF and reduced ejection fraction.[77] The role of RHR in HF is especially significant on account of its significance for clinical treatment in these patients. Both sympathetic and renin-angiotensin-aldosterone systems overactivity is mainly responsible for the relationship between RHR and HF. The reasons behind this association are increased oxygen consumption, decreased myocardial perfusion, and consequently decreased cardiac performance (hemodynamic changes and ultimately pro-arrhythmic effect. An additional mechanism that explains the relationship between RHR and mortality in HF is inflammation, endothelial dysfunction, and increased oxidative stress. Woodward *et al*. reported that patients with RHR >80 bpm had a 2-time higher risk of HF death than individuals with RHR <65 bpm. Whereas the Rotterdam study uncovered that every increase of 10 bpm increased the risk of development of HF for 16% in men.[69]

RHR is similarly very important for the prognosis of patients after MI. According to the meta-analysis that included around 20,000 patients from GISSI preliminaries, demonstrated the in-hospital mortality of patients after MI with HR <60 bpm was essentially lower than in patients when HR rises >100 bpm (3.3% *vs* 10.1%).[69] Whereas data from the PERFORM study, including 19,000 patients uncovered that RHR ≥70 bpm was related to 32% increased relative risk for fatal or nonfatal MI (HR 1.32; 95% CI: 1.03–1.69). Every 5-bpm RHR increment raised the relative risk for fatal and nonfatal MI by 11.3%. These findings revealed that in patients with recent non-cardio-embolic cerebral ischemia event, raised RHR ≥70 is a prognostic factor and is related to a higher risk for MI.[78]

Elevated RHR has been demonstrated to be prognostically connected with adverse events across several population studies. In the acute setting in patients with acute MI, raised HR has been additionally demonstrated to be related to poor results both in the prethrombolytic and contemporary eras. An HR >80 bpm at the time of admission was related to 3–5 times the danger of mortality compared to lower HR. Regardless of the reality that the treatment has improved fundamentally during recent years; there is still a significant relationship between increased HR at admission and increased in-hospital mortality.[4] Hjalmarson *et al*. identified in 1807 patients with acute MI, the connection between HR on hospital admittance and after discharge from the hospital and respectively total mortality from admittance to discharge and mortality at 1 year. It was observed in the study that the in-hospital mortality and post-discharge mortality increased with elevated HR on admittance. Likewise, the total mortality was found to be 15% for patients with an admittance HR in the range of 50 and 60 bpm, 41% for HR 90 bpm, and 48% for HR >110 bpm. Mortality from hospital discharge to 1 year was additionally identified with the maximal HR in the coronary care unit and to HR at discharge. In patients with moderate HF, the combined mortality for patients with an admittance HR of ≥90 bpm was more than twice that of patients with an admittance HR of 90 bpm (39% *vs* 18%). A comparative relationship was also seen in patients with mild or no HF (18% *vs* 10%).[79,80]

The prognostic implication of HR was similarly assessed in 8,915 patients with acute MI of the GISSI-2 study, treated with fibrinolytic treatment. In this examination, elevated HR on admittance was related to a progressive increment of in-hospital mortality (7.1% for HR <60 bpm to 23.4% for HR >100 bpm). A dynamic increase of 6-month mortality was noted with elevated HR (0.8% for HR <60 bpm to 14.3% for HR

>100 bpm). The multivariate assessment indicated that HR was an independent prognostic factor of mortality. Similar results were observed in the Secondary Prevention Reinfarction Israeli Nifedipine Trial (SPRINT), performed before the thrombolytic era, which demonstrated that HR on admittance in the coronary care unit was related to total mortality and the events of complications.[79]

Whereas according to a prospective, multicenter study, structured to examine the predominance of Prevalence of Peripheral Arterial Disease in Patients with Acute Coronary Syndrome (PAMISCA), an RHR ≥70 bpm in patients who have an Acute Coronary Syndrome (ACS) is an indicator of a high risk of suffering CV events during follow-up. It was discovered in the study that patients with HR ≥70 bpm had poorer prognosis, with additional hospitalizations for HF and higher CV and non-CV mortality rates, while in the multivariate analysis, HR ≥70 bpm has independently corresponded with mortality during follow-up (HR: 2.5; 95% CI: 1.26–4.97, $p = 0.009$), alongside peripheral artery disease during hospitalization, ejection fraction <40%, age, and T2D. These findings from the study revealed that the baseline HR is directly and independently related to ischemic events, sudden death, CV death, and mortality from any cause, both in patients with known ischemic events and in the normal population or patients with increased CV risk.[81]

Elevated RHR is an easily measured clinical finding in patients with stable recurring HF and sinus rhythm. But in patients with mild to severe chronic HF, raised RHR is associated with an increased risk of all-cause mortality (ACM) and CV mortality. It was known that the decrease in HR improves clinical outcomes in patients with recurring HF and in sinus rhythm, but the relationship between HR and post-discharge outcomes in patients with HHF (hospitalized for HF) is presently unclear. According to the post-hoc analysis of the Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan (EVEREST) trial study, in patients with HHF in presumed sinus rhythm, higher RHR in the early post-discharge period was independently associated with increased mortality during subsequent follow-up. It was discovered that, at HR ≥70 bpm, each 5-beat increase in 1-week post-discharge HR was independently related with increased all-cause mortality [HR: 1.13 (95% CI: 1.05 to 1.22); $p = 0.002$]. While, each 5-beat increment ≥70 bpm in 4-week post-discharge HR was foretelling all-cause mortality [HR: 1.12 (95% CI: 1.05 to 1.19); $p = 0.001$]. These findings revealed that HR at the time of discharge was found to be predictive of death within 100 days post-randomization.[82]

In the Basel Stent Kosten-Effektivitats Trial-Prospective Validation Examination (BASKETPROVE) study, including 2,029 patients who had gone through percutaneous coronary intervention (PCI) for ST-elevation myocardial infarction (STEMI) and non-ST-segment elevation acute coronary syndromes (NSTE-ACS), it was found that the mortality rises with the elevations in HR. Patients with an HR between 60 bpm and 89 bpm had a 4-fold increment in mortality contrasted with patients in the lowest HR category (<60 bpm) and those patients who were discharged with an HR above 90 bpm had a 17-fold increment in mortality contrasted with patients below 60 bpm. Conversely, none of the STEMI patients discharged with an HR below 60 bpm died during follow-up. Accordingly, it can be inferred from the investigation that elevated HR at discharge was associated with long-term all-cause mortality as well as CV deaths and nonfatal MI in "all-comer" patients going through PCI independent of ailment introduction, for example, stable angina pectoris, NSTE-ACS, and STEMI.[48,3]

The comparable outcome was found in a Dutch population of STEMI patient's as Basket prove study, an HR above 70 bpm *vs* HR below 70 bpm was related with a hazard ratio of 3.2 (1.4–7.0) for ACM, and 2.4 (1.0–5.8) for CV mortality.[4]

Take Home Pearls

- RHR is a non-invasively measured marker of cardiac function and a good indicator of physical wellness and general well-being.
- Increased RHR is related to endothelial dysfunction, reduced artery compliance, and distensibility, and consequently increased arterial wall stress and elevated pulsed-wave velocity, which are further, related to increase after burden and at last fundamental HTN.
- In acute MI, raised HR has been additionally demonstrated to be related to the poor outcomes both in the prethrombolytic and contemporary eras.
- In patients with coronary artery disease, high RHR incites CV events mainly through ventricular arrhythmias or progressive pump failure.
- In patients with mild to severe recurring HF, raised RHR is related to an increased risk of ACM and CV mortality.

Take Home Summary

RHR is an easily accessible parameter impacted by many physiological and pathological conditions. HR is mainly regulated by the sympathetic and parasympathetic input of ANS. HR varies according to age, sex, weight/BMI, and rest. Cardiac conduction system (CCS) is divided into the impulse-generating nodes (SA Node and AV Node) and the impulse-propagating His-Purkinje system. Out of all the channels, I_f plays a major role in the generation of pacemaker activity and the regulation of HR. HR and HRV both are risk markers in cardiac disease. HRV reflects beat-to-beat changes in RR intervals, which are related to the ongoing interplay between two arms of the ANS. It is also an index of the sympathovagal modulation of HR. A high HRV is a sign of a healthy heart, whereas a reduced HRV is a symptom of health problems and can affect immune functions, self-regulation, and psychological abilities. Traditionally, HR is measured by pulse palpation, but other methods can be used to measure HR, such as ECG- and PPG-based wearable devices. RHR has a wide variation across the world. Indian population shows an increased RHR because of their increased SO. RHR is strongly associated with longevity, and HRV is linked to various cardiometabolic diseases.

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