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INTERNATIONAL

Sinus Bradycardia: Normal Phenomenon or Risk Factor? Evaluation Based on Recent Evidence

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Although sinus bradycardia is a common abnormality seen in medical reports, the proper evaluation of sinus bradycardia is poorly understood by physicians. Recent data from heart rate epidemiologic and cohort studies has emerged regarding the risk stratification of sinus bradycardia, which may help insurers better underwrite this abnormality. In this review, an operational age-related heart rate reference based on recent advances is provided along with a suggested approach to the risk stratification and assessment of prognosis for inappropriate sinus bradycardia.

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Measurement of heart rate (HR) is fundamental to the assessment of an individual's pathophysiological status. Not only for the diagnosis and treatment for arrhythmias, but an individual's heart rate may indicate whether the person is likely to be at increased risk for adverse outcomes.

The normal range for heart rate in adults was established as 60–100 beats per minute (bpm) decades ago.[1] Sinus bradycardia has long been said to exist in adults with a sinus rhythm of less than 60 bpm. A rate above 100 per minute is called sinus tachycardia. These normal limits (60–100 bpm) and terminologies are used in guidelines or textbooks principally for convenience and for uniformity of designation. Evidence underpinning these limits is scarce.

Sinus bradycardia is common in young healthy adults, during sleep, and in elite athletes. Increasing evidence has shown the protective role of low heart rate for cardiovascular outcomes as compared with high heart rate.[2] Marked sinus bradycardia is often considered to be a marker of sinus node dysfunction (SND),[3] and may be a risk

Table 1. Heart Rate of Reference Range Subset

	Both sexes			Male			Female		
Group	median	2%–98%	1%–99%	median	2%–98%	1%–99%	median	2%–98%	1%–99%
ALL	68	48–98	46–103	66	47–98	45–103	68	49–98	47–103
0–9	84	60–120	58–129	83	59–116	57–127	86	62–126	60–133
10–19	70	49–101	47–105	70	48–99	47–106	71	52–101	50–104
20–29	66	46–94	43–98	63	44–91	42–97	69	49–96	46–99
30–39	68	48–95	46–99	66	47–95	44–100	69	50–95	48–99
40–49	68	49–97	47–102	67	47–97	45–101	69	50–97	48–103
50–59	68	49–98	47–102	68	48–98	46–103	68	49–97	47–102
60–69	67	48–98	45–103	67	47–99	45–104	68	49–97	47–102
70–79	65	46–93	44–99	63	45–94	43–100	66	47–93	45–98
80–89	64	47–89	45–96	61	46–87	44–95	65	48–91	47–96
90–99	66	47–95	47–95	59	48–95	48–95	68	47–94	47–94

Note: Reference range subset included 46,129 subjects from 57 countries, 6 continents. Cardiac or metabolic disorders were excluded. The subjects were supine and at rest for at least 5 minutes before recording.

Adapted from: Mason et al. *J Electrocardiology*. 2007;40:228–234. Permission given by Dr. Mason and *Elsevier*.

factor for sudden cardiac death.[4] Thus, two questions arise: is sinus bradycardia a normal phenomenon, or is it a risk factor? Should we continue to evaluate sinus bradycardia by the current commonly used reference? In this article, we will review recent findings with regard to the evaluation of sinus bradycardia.

NORMAL RHYTHM VS SINUS BRADYCARDIA - RECONSIDERATION OF THE REFERENCE RANGES

Decades ago, Spodick et al challenged the traditional operational definitions for sinus bradycardia and tachycardia. From a population of 500 asymptomatic subjects aged 50 to 80 years, the normal range of resting heart rate was estimated to be 46–93 bpm in men and 51–95 bpm in women.[5] Spodick proposed the appropriate rate range for sinus rhythm should be 50–90 bpm.

There are few large population-based studies available for assessing the age- and sex-related heart rate reference ranges, especially those based on modern electrocardiographic technology. Recently, several studies of normal heart rate reference ranges using ECG measurements derived from simultaneously recorded ECGs have been published.[6–9] In a healthy Chinese population, 15% had a heart rate <60 bpm, with a prevalence of 18% in men and 9% in women.[7] In a study conducted in 6 continents, baseline ECGs of 79,743 individuals were surveyed and a subgroup of 46,129 individuals with a very low probability of cardiovascular disease was identified.[9] The normal heart rate ranged from 48–98 bpm using the 2nd and 98th percentiles (Table 1). This provides important insight for the reconsidering normal resting heart rate related to the influence of age and sex. The authors state that sinus bradycardia is over diagnosed with the current reference limit (<60 bpm).

It is a different picture in pediatrics, since reference ranges published by different international organizations vary greatly.[10–13] What adds to the challenge is that infancy and childhood are periods of enormous physiological and developmental changes. Fortunately, a recent study has systematically reviewed and synthesized data from over 140,000 healthy children in 69 studies to create new centile charts for heart rate.[14] Through comparison of the centile charts with existing guidelines (APLS,[10] PALS,[11] PHTLS,[12] ATLS[13] and EPLS[15]), it can be found in children of 2–18 years old that the

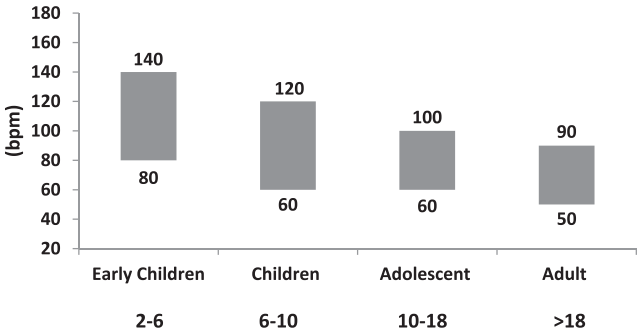


Figure 1. *Proposed reference of normal heart rate range by age periods.*

lower limit of PHTLS is reasonable, and the upper limit of APLS is more matchable.

We propose a heart rate reference based on the recent advances and on consideration of operational simplicity (Figure 1). According to Mason's survey, the upper limit of heart rate in an adult might be 100 bpm.[9] However, recent studies have revealed that the relative risk of high heart rate on all-cause and cardiovascular mortality in either healthy population or cardiovascular patients begins to increase at >90 bpm or even >80 bpm.[2,16,17] The upper threshold of 90 bpm would improve risk evaluation. Further discussion of this component of the heart rate range is beyond the scope of this article. We think the proposed reference for different age groups would benefit risk selection.

Corresponding to current advances on epidemiological evidences, several recently published guidelines have revised the definition of sinus bradycardia to a lower threshold (Table 2).[18–20] A new definition should improve the diagnostic specificity of sinus bradycardia.

RISK STRATIFICATION OF LOW HEART RATE

Among mammals, there is an inverse relation between heart rate and life expectancy. Arctic whales live as many as 150 years, hamsters an average 3 years. Whales can have heart rates as few as 10 bpm, whereas hamsters as many as 450 bpm. It is common knowledge that long-term exercise is associated with a relatively low heart rate, and is associated with improved health and, therefore, life expectancy.

However, it also raises the question as to whether a low heart rate is a risk factor in certain conditions. First, it can reduce coronary perfusion pressure, especially in the elderly with stiff vasculature and widened pulse pressure. Chronic insufficient perfusion may induce or aggravate cardiovascular disease. Furthermore, if symptoms (ie, syncope, fatigue, dizziness or dyspnoea) accompany sinus bradycardia, examination for SND or other diseases is required.

Comparative analysis of current studies suggests the existence of certain higher risk groups with low heart rate (Table 3). In a normal population, CVD, CHD, and total mortality rates increased with each successive increase in RHR (resting heart rate) quintile.[2] However, in certain populations, the linear relationship between the heart rate and mortality was only found for heart rate above 60 bpm, resulting in a J-shaped relationship. In women, mortality of CVD and stroke in the 65–79 and 80–94 bpm groups was significantly lower than in the

Table 2. Definitions of Sinus Bradycardia from Several Recently Published Guidelines

Sponsor	Year	Guidelines	Definition	Ref.
ACP (US)	2003	Training and Competency Evaluation for Interpretation of 12-Lead Electrocardiograms	<50 bpm	18
ESC (Europe)	2009	Guidelines for the diagnosis and management of syncope	<50 bpm	19
AHA (US)	2010	Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care	<50 bpm	20

ACP: American College of Physicians. ESC: European Society of Cardiology. AHA: American Heart Association.

Table 3. Selected Studies of the Relationship Between Resting Heart Rate and Cardiovascular or All-cause Mortality in Different (Patient) Populations

Study (ref.)	Baseline characteristics	Sample	Heart rate categories (bpm)	Selected findings
National FINRISK Study, Finland[2]	Random sample of population	10 519 men, 11 334 women, age 25–74 with a 6–27 years follow-up	men: ≤60, 62–66, 68–72, 74–80, ≥82. women: ≤64, 66–68,70–74, 76–80, ≥82	On univariable analysis CVD, CHD, and total mortality rates increased with each successive increase in RHR quintile (Linear)
3C Study, France[22]	Elderly population	7 147, 39% men, age≥65 with a mean follow-up of 4.9 years	<62, 62–67.5, 68–72.5, 73–79, >79	J-Shaped in CAD incidence rate, lowest in 62–67.5 bmp group
CORDIS study, Israel[23]	Industrial employees	3 527 men, mean age 45, 75% Blue-collar, 8 years follow-up	<70, 70–79, 80–89, ≥90	J-Shaped pronounced in CVD and cancer mortality, lowest in 70–79 bmp group
ARIC, US[24]	With prehypertension	3 275, 49% men, age 45–64 with a mean follow-up of 10.1 years	<60, 60–69, 70–79, ≥80	No difference between <60 and 60–69 groups in all-cause mortality over all sex. But in males, CHD risk is higher in <60 group than 60–69 group
Glasgow, UK[25]	With hypertension	4 065, 47% men, mean age≈51 with a mean follow-up of 897 days	≤60, 61–70, 71–80, 81–90, ≥91	J-Shaped pronounced in CVD and IHD mortality, lowest in 61–70 bpm
INVEST, multi-national[26]	With hypertension and CAD	22 192, 47.8% men, age>50 with a mean follow-up of 2.7 years	≤50, 51–55, 56–60, 61–65, 66–70, 71–75, 76–80, 81–85, 86–90, 91–95, 96–100, >100	J-Shaped in adverse outcomes, more pronounced in diabetes and prior MI, nadir 59bpm in all cohort, nadir 64bpm in prior MI
CRUSADE, US[27]	with non-ST segment elevation ACS	135 164, 59.7% men, age 67±14	<50, 50–59, 60–69, 70–79, 80–89, 90–99, 100–109, 110–119, 120–129, >130	Risk of all-cause mortality and stroke was significantly higher in the group with a presenting HR <50 bpm even after controlling for baseline variables, Compared with the reference group (60–69 bpm); J-shaped

CAD: coronary artery disease CVD: cardiovascular disease IHD: ischemic heart disease SBP: systolic blood pressure MI: myocardial infarct ACS: acute coronary syndromes.

<65 bpm group. A similar trend occurred in men but was not statistically significant.[21] The J-shaped relationship was also found in elderly, industrial employees and patients with prehypertension, hypertension or cardiovascular disease.[22–27] In the CRUSADE study of patients with non-ST-segment elevated acute coronary syndrome, a clear J-shaped correlation was found between resting heart and all-cause mortality.[27] The lowest mortality rate was in patients with resting heart rate between 50–70 bpm, but mortality doubled when heart rate was below 50 bpm. It appeared that the more severe the cardiovascular disorder, the greater the risk of bradycardia.

Table 4. Etiologies of Sinus Bradycardia

Irreversible (physiological)	**Reversible (functional)**
Aging	Cardiac medications
Endurance training	β-Adrenergic blockers
	Calcium-channel blockers
Irreversible (pathological)	Clonidine
Idiopathic degeneration	Digoxin
(Sclero-degenerative-fibrotic disease)	Antiarrhythmic agents
Myocardial Infarction	Methyldopa
Coronary heart disease	Procainamide
Cardiomyopathies	Disopyramide
Valvular heart diseases	Lithium
Infiltrative	Quinidine
Fatty replacement	Amiodarone
Fibrosis	Hypervagotonia
Sarcoidosis	Vasovagal syncope
Amyloidosis	Carotid sinus hypersensitivity
Hemochromatosis	Intracranial hypertension
Collagen vascular diseases	Situational disturbances
Systemic lupus erythematosus	Coughing
Rheumatic carditis	Vomiting
Scleroderma	Defecation
Inflammatory	Micturition
Chagas' disease	Hypothermia
Typhoid	Hypothyroidism
Endocarditis	Hypoglycemia
Surgical trauma	Electrolyte imbalances
Valve replacement	Hypokalemia
Correction of congenital heart disease	Hyperkalemia
Heart transplantation	Peptic ulcer
Myotonic muscular dystrophy	Nicotine abuse
Congenital sinus node abnormalities	Sleep apnea

MORTALITY

No studies have estimated the prognostic significance of asymptomatic bradycardia and its impact on all-cause mortality until recently.[28] Jeffrey et al evaluated the need for subsequent pacemaker implantation and mortality in older outpatients (>60) with or without bradycardia. The cohort consisted of 2560 patients, of whom 470 had asymptomatic bradycardia. The bradycardia group consisted of 66% patients with 50–54 bpm, 24% with 45–49 bpm, 8% with 40–44 bpm, and 3% with <40 bpm. A very low rate of subsequent pacemaker implantation was recorded for asymptomatic bradycardia, annualized to <1% per year. Asymptomatic bradycardia had no adverse impact on all-cause mortality. Nevertheless, variables such as aging, male gender, atrial fibrillation, and abnormal QRS significantly predicted all-cause mortality.[28] The limitation of this study lies in the information missing on medication and cardiac disease, and that the vast majority had rate >40 bpm.

ETIOLOGY OF SINUS BRADYCARDIA AND ASSOCIATED DISORDERS

Etiology

A classification of sinus bradycardia is introduced here. Sinus bradycardia is regarded as either reversible or irreversible with the latter divided into physiological and pathological (Table 4). Aging is a critical risk

factor for sinus bradycardia if other causes can be ruled out. In normal healthy humans, the intrinsic heart rate (the heart rate without any autonomic input) declines from 107 bpm at 25 years to 90 bpm at 50 years, then to 70 bpm at 85 years.[29] Pathologically irreversible bradycardia is characterized by the replacement or infiltration of nodal tissue especially with fibrous tissues. Permanent injury can also occur due to cardiac surgery. Cardiac medications are the most common causes of reversible bradycardia. Since sinus rhythm is constrained by vagal tone, extrinsic causes which enhance vagal reflex activity may also contribute to sinus bradycardia.

The value of this classification of etiologies of sinus bradycardia is its simplicity, clarity and thus conformity to risk evaluation in life insurance. A risk stratification flowchart based on this classification will be discussed later (Figure 2).

Sinus Node Dysfunction

Sinus node dysfunction (SND), also referred to as ''sick sinus syndrome,'' is a common cause of sinus bradycardia.[3] It is an electrocardiographically defined group of abnormalities that include: marked sinus bradycardia (<40 bpm), sinoatrial arrest, sinoatrial exit block, and bradycardia-tachycardia syndrome. If acquired cardiac conditions and other reversible etiologies can be ruled out, the most important differential diagnosis is often idiopathic SND.

Since patients with SND are often asymptomatic, its precise prevalence has not been well quantified. One index for the incidence of the SND is the rate with which cardiac pacemakers are implanted for this condition. The incidence of new pacemaker implants is about 150 per million populations across the world (~700 in Europe and United States). SND accounts for approximately 30%–50% of the pacemaker implantations.[30]

Suspected patients with mild or moderate sinus bradycardia or symptoms are often evaluated for SND with Holter electrocardiographic recording. A threshold of 50 bpm was found by Holter recording to suggest SND.[31] In the Theopace study,[32] patients were included for detection of SND if they met all the following criteria: (1) age ≥45; (2) mean sinus rate at rest <50 bpm and/or intermittent sinoatrial block in >1 standard electrocardiogram recorded during diurnal hours on different days; (3) symptoms attributable to SND such as syncope or dizziness, and/or easy fatigue or effort dyspnea.

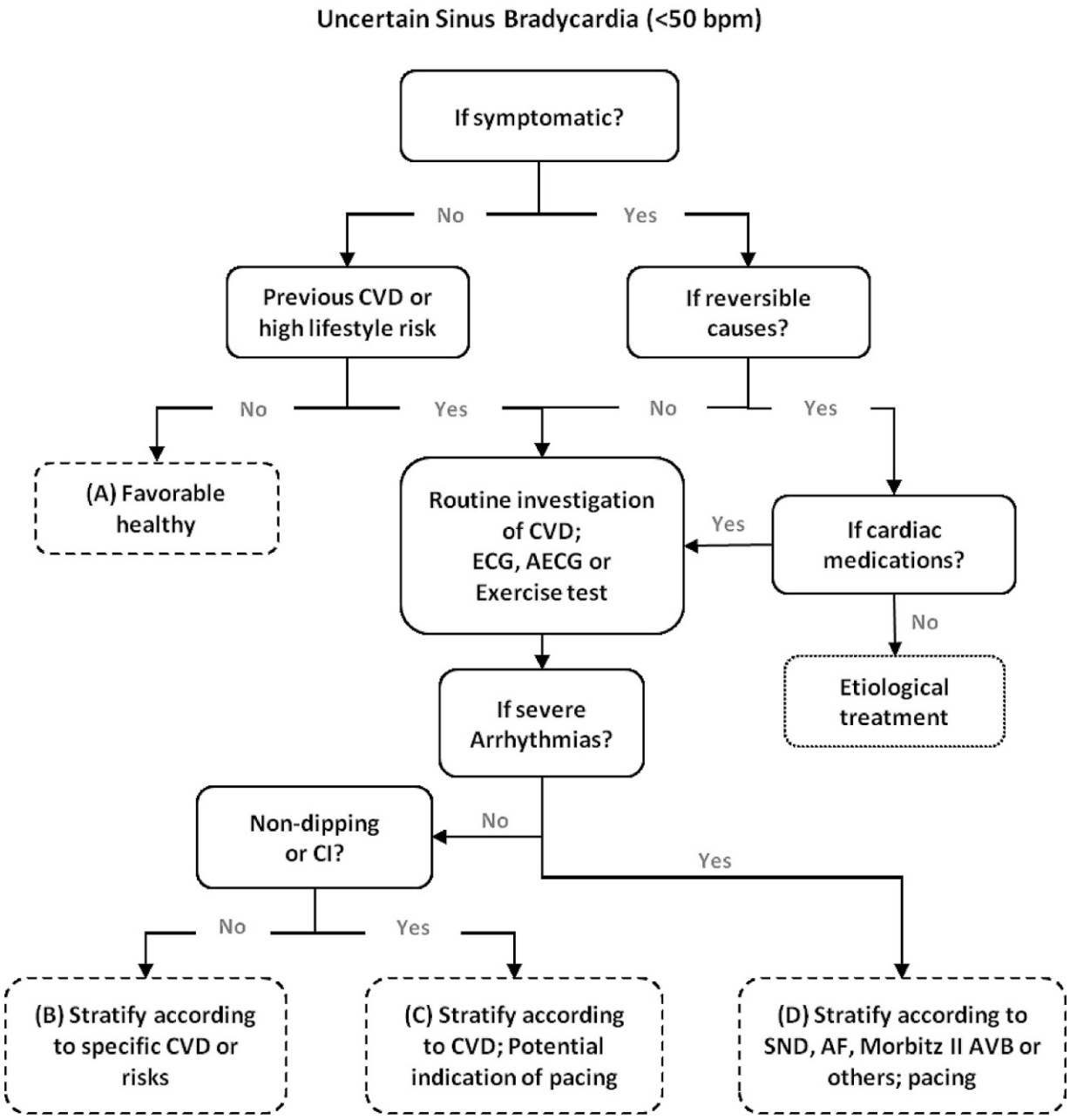
Variations in Automatic Nervous System

The low heart rate response to exercise is recently regarded as ''chronotropic incompetence,'' and blunted heart rate response during circadian cycle has been termed ''nocturnal non-dipping.'' Abnormal heart rate variation has been reported to be associated with advanced target organ damage and further CVD events.

Chronotropic Incompetence

Chronotropic incompetence (CI), broadly defined as the inability of the heart to increase its rate commensurate with increased activity or demand, is common in patients with cardiovascular disease. Using <80% of APMHR (age-predicted maximal heart rate, usually based on the 220 – age equation) as the criterion, approximately 25%–75% of heart failure patients demonstrate CI.[33] Besides APMHR, there are other measures for CI including the following: (1) absolute HR achieved at the end of stage 2 of exercise stress test; (2) absolute peak HR achieved with maximal exercise stress testing; (3) HR reserve ($HR_{peak} - HR_{rest}$); (4) peak HR ≥1 SD below the mean HR achieved for age by cohort; (5) chronotropic index [$(HR_{peak} - HR_{rest})/ (220 - age - HR_{rest})$].[34,35]

CI has been considered as an independent predictor of major adverse cardiovascular events and overall mortality even in health asymptomatic people.[35–37] Those who were chronotropically incompetent were significantly older, hypertensive, more likely to



Note: Cardiovascular disease (CVD); electrocardiogram (ECG); ambulatory electrocardiogram (AECG); chronotropic incompetence (CI); sinus node dysfunction (SND); atrial fibrillation (AF); atrioventricular block (AVB).

Figure 2. *Flowchart for the risk evaluation of uncertain sinus bradycardia.*

smoke, had a greater body mass index, higher total cholesterol, lower HDL, and ultimately had a higher Framingham Risk Score.[35] Commonly used cardiovascular medications, including β-blockers, digitalis, certain calcium channel blockers, amiodarone, and others, can confound the determination of CI. Rate-adaptive pacing has been shown to enhance functional capacity in patients with CI.[38]

Nocturnal Non-dipping

Heart rate during sleep is lower than during daytime. Heart rate nondipping is defined as follows: (average awake value −

average sleep value)/average awake value <10% (in other words, the sleep dip is less than 10%). The dipping pattern is now considered to be a better predictor of CVD events than resting heart rate.[39]

Non-dipping of heart rate showed a significant relationship with both cardiovascular events and all-cause mortality (CVD HR: 3.00, P=0.001; all-cause mortality HR=2.38, P=0.028, vs dipping) in hypertensive patients.[39] In multivariable analyses, the risk of CVD events in the non-dipping group is almost the same as that of the diabetes group. Older individuals, smokers, women, subjects with a higher BMI, and patients treated for diabetes or hypertension had less dipping.[40]

MEASUREMENTS

The standard ECG is not a sensitive measurement for the investigation of sinus bradycardia. Since the key to prognostic evaluation lies in the cause-and-effect relationship between symptoms and bradycardia, ambulatory 24–48 hours electrocardiographic recording is particularly useful.[41] Ambulatory monitoring also helps with the diagnosis of SND and abnormal heart rate variation. External or implantable intermittent recorders offer further advantage for subjects with less frequent symptoms.[42]

An exercise ECG is often considered for cardiovascular risk assessment in asymptomatic subjects. Atropine and isoproterenol tests are also reliable measurements of asymptomatic sinus bradycardia.[43]

The diagnostic sensitivity of electrophysiologic testing in subjects with symptoms caused by bradycardia is limited, because it may sometimes reveal unrelated rhythm disturbances that may mistakenly be designated as the cause of the syncope.[44]

EVALUATION

Sinus bradycardia with resting HR over 50 bpm should not be considered as abnormal as discussed above. Heart rate below 40 bpm, either symptomatic or asymptomatic, is usually investigated because of the risk of low coronary perfusion or SND. For sinus rate between 40 to 50 bpm, distinguishing between physiologic and pathologic is the key component of evaluating sinus bradycardia and often confuses physicians. Possible causes are sought in a comprehensive investigation of the history and physical examination. Ambulatory electrocardiography is performed when differential diagnosis is needed.

Nevertheless, the evaluation of the risk of sinus bradycardia depends on full profiles rather than absolute heart rate limits. A systematic approach to risk evaluation of sinus bradycardia should identify potentially correctable or reversible causes, heart rate variation, underlying pathological alteration, coexisting severe arrhythmias and SND. Following this strategy, a flowchart for the risk stratification of uncertain sinus bradycardia has been designed (Figure 2). Using this, subjects with sinus bradycardia can be stratified into 4 major levels with graded risk: (a) favourable healthy; (b) specific CVD; (c) specific CVD and potential pacing; and (d) severe risk and pacing.

Factors that increase the risk of heart disease may also increase the risk of bradycardia. Adverse lifestyle factors such as: high cholesterol, smoking, heavy alcohol use, use of illegal drugs, psychological stress or anxiety and physical inactivity may prompt investigation for underlying CVD.

SUMMARY

Commonly accepted reference ranges for heart rate have been in use with little change over many decades. Sinus bradycardia conventionally defined as <60 bpm is too common an abnormality. According to recent epidemiologic studies, reduction of the sinus heart rate threshold from 60 bpm to 50 bpm would improve the specificity of bradycardia detection. On the other hand, recent findings on the potential risk associated with low heart

rate suggest a systematic approach to the evaluation of sinus bradycardia should cover correctable or reversible causes, heart rate variation, underlying pathological alteration, coexisting severe arrhythmias and SND. Re-examination of sinus bradycardia should contribute to improved risk stratification.

REFERENCES

1. Kossmann CE. The normal electrocardiogram. *Circulation*. 1953;8:920–936.
2. Cooney MT, Vartiainen E, Laatikainen T, Juolevi A, Dudina A, Graham IM. Elevated resting heart rate is an independent risk factor for cardiovascular disease in healthy men and women. *Am Heart J*. 2010;159:612–619.
3. Brignole M. Sick sinus syndrome. *Clin Geriatr Med*. 2002;18:211–227.
4. Epstein AE, Carlson MD, Fogoros RN, Higgins SL, Venditti FJ Jr. Classification of death in antiarrhythmia trials. *J Am Coll Cardiol*. 1996;27:433–442.
5. Spodick DH, Raju P, Bishop RL, Rifkin RD. Operational definition of normal sinus heart rate. *Am J Cardiol*. 1992;69:1245–1246.
6. Rijnbeek PR, Witsenburg M, Schrama E, Hess J, Kors JA. New normal limits for the paediatric electrocardiogram. *Eur Heart J*. 2001;22:702–711.
7. Wu J, Kors JA, Rijnbeek PR, van Herpen G, Lu Z, Xu C. Normal limits of the electrocardiogram in chinese subjects. *Int J Cardiol*. 2003;87:37–51.
8. Al-Safi SA, Otoom SA. Distribution of blood pressure and heart rate among adults in Jordan: A national survey. *Clin Exp Hypertens*. 2005;27:467–475.
9. Mason JW, Ramseth DJ, Chanter DO, Moon TE, Goodman DB, Mendzelevski B. Electrocardiographic reference ranges derived from 79,743 ambulatory subjects. *J Electrocardiol*. 2007;40:228–234.
10. Mackway-Jones K, Advanced Life Support Group (Manchester England). *Advanced paediatric life support: The practical approach*. Malden, Mass: Blackwell; 2005.
11. Ralston M, American Heart Association, American Academy of Pediatrics. *Pals provider manual*. Dallas, Tex: American Heart Association; 2006.
12. National Association of Emergency Medical Technicians (US). Pre-Hospital Trauma Life Support Committee, American College of Surgeons. Committee on Trauma. Phtls–basic and advanced prehospital trauma life support. 2003:xviii, 426 p. ill. (chiefly col.) 427 cm. + 421 CD-ROM (424 423/424 in.).
13. *Advanced trauma life support for doctors atls: Manuals for coordinators and faculty*. Chicago, IL: American College of Surgeons; 2008.
14. Fleming S, Thompson M, Stevens R, et al. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: A systematic review of observational studies. *Lancet*. 2011;377:1011–1018.
15. Biarent D, Bingham R, Eich C, et al. European resuscitation council guidelines for resuscitation 2010 section 6. Paediatric life support. *Resuscitation*. 2010;81:1364–1388.
16. Bohm M, Swedberg K, Komajda M, et al. Heart rate as a risk factor in chronic heart failure (shift): The association between heart rate and outcomes in a randomised placebo-controlled trial. *Lancet*. 2010;376:886–894.
17. Zhang X, Shu XO, Xiang YB, et al. Resting heart rate and risk of type 2 diabetes in women. *Int J Epidemiol*. 2010;39:900–906.
18. Salerno SM, Alguire PC, Waxman HS. Training and competency evaluation for interpretation of 12-lead electrocardiograms: Recommendations from the american college of physicians. *Ann Intern Med*. 2003;138:747–750.
19. Moya A, Sutton R, Ammirati F, et al. Guidelines for the diagnosis and management of syncope (version 2009). *Eur Heart J*. 2009;30:2631–2671.
20. Neumar RW, Otto CW, Link MS, et al. Part 8: Adult advanced cardiovascular life support: 2010 american heart association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2010;122:S729–767.
21. Tverdal A, Hjellvik V, Selmer R. Heart rate and mortality from cardiovascular causes: A 12 year follow-up study of 379,843 men and women aged 40–45 years. *Eur Heart J*. 2008;29:2772–2781.
22. Legeai C, Jouven X, Tafflet M, et al. Resting heart rate, mortality and future coronary heart disease in the elderly: The 3c study. *European Journal of Cardiovascular Prevention and Rehabilitation: Official Journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology*. 2011.
23. Kristal-Boneh E, Silber H, Harari G, Froom P. The association of resting heart rate with cardiovascular, cancer and all-cause mortality. Eight year follow-up of 3527 male israeli employees (the cordis study). *Eur Heart J*. 2000;21:116–124.
24. King DE, Everett CJ, Mainous AG, 3rd, Liszka HA. Long-term prognostic value of resting heart rate in subjects with prehypertension. *Am J Hypertens*. 2006;19:796–800.
25. Paul L, Hastie CE, Li WS, et al. Resting heart rate pattern during follow-up and mortality in hypertensive patients. *Hypertension*. 2010;55:567–574.
26. Kolloch R, Legler UF, Champion A, et al. Impact of resting heart rate on outcomes in hypertensive patients with coronary artery disease: Findings

from the international verapamil-sr/trandolapril study (invest). *Eur Heart J*. 2008;29:1327–1334.
27. Bangalore S, Messerli FH, Ou FS, et al. The association of admission heart rate and in-hospital cardiovascular events in patients with non-st-segment elevation acute coronary syndromes: Results from 135,164 patients in the crusade quality improvement initiative. *Eur Heart J*. 2010;31:552–560.
28. Goldberger JJ, Johnson NP, Gidea C. Significance of asymptomatic bradycardia for subsequent pacemaker implantation and mortality in patients >60 years of age. *Am J Cardiol*. 2011.
29. Opthof T, Coronel R. The normal range and determinants of the intrinsic heart rate in man. *Cardiovasc Res*. 2000;45:175–176.
30. Mond HG, Proclemer A. The 11th world survey of cardiac pacing and implantable cardioverter-defibrillators: Calendar year 2009-a world society of arrhythmia's project. *Pacing Clin Electrophysiol*. 2011;34:1013–1027.
31. Reiffel JA, Bigger JT Jr, Cramer M, Reid DS. Ability of holter electrocardiographic recording and atrial stimulation to detect sinus nodal dysfunction in symptomatic and asymptomatic patients with sinus bradycardia. *Am J Cardiol*. 1977;40:189–194.
32. Menozzi C, Brignole M, Alboni P, Boni L, Paparella N, Gaggioli G, Lolli G. The natural course of untreated sick sinus syndrome and identification of the variables predictive of unfavorable outcome. *Am J Cardiol*. 1998;82:1205–1209.
33. Roche F, Pichot V, Da Costa A, Isaaz K, et al. Chronotropic incompetence response to exercise in congestive heart failure, relationship with the cardiac autonomic status. *Clin Physiol*. 2001;21:335–342.
34. Wilkoff BL, Miller RE. Exercise testing for chronotropic assessment. *Cardiol Clin*. 1992;10:705–717.
35. Gulati M, Shaw LJ, Thisted RA, Black HR, Bairey Merz CN, Arnsdorf MF. Heart rate response to exercise stress testing in asymptomatic women: The St. James women take heart project. *Circulation*. 2010;122:130–137.
36. Jouven X, Empana JP, Schwartz PJ, Desnos M, Courbon D, Ducimetiere P. Heart-rate profile during exercise as a predictor of sudden death. *N Engl J Med*. 2005;352:1951–1958.
37. Adabag AS, Grandits GA, Prineas RJ, Crow RS, Bloomfield HE, Neaton JD. Relation of heart rate parameters during exercise test to sudden death and all-cause mortality in asymptomatic men. *Am J Cardiol*. 2008;101:1437–1443.
38. McElroy PA, Janicki JS, Weber KT. Physiologic correlates of the heart rate response to upright isotonic exercise: Relevance to rate-responsive pacemakers. *J Am Coll Cardiol*. 1988;11:94–99.
39. Eguchi K, Hoshide S, Ishikawa J, et al. Nocturnal nondipping of heart rate predicts cardiovascular events in hypertensive patients. *J Hypertens*. 2009;27:2265–2270.
40. Ben-Dov IZ, Kark JD, Ben-Ishay D, Mekler J, Ben-Arie L, Bursztyn M. Blunted heart rate dip during sleep and all-cause mortality. *Arch Intern Med*. 2007;167:2116–2121.
41. Sarasin FP, Carballo D, Slama S, Louis-Simonet M. Usefulness of 24-hr holter monitoring in patients with unexplained syncope and a high likelihood of arrhythmias. *Int J Cardiol*. 2005;101:203–207.
42. Paruchuri V, Adhaduk M, Garikipati NV, Steinberg JS, Mittal S. Clinical utility of a novel wireless implantable loop recorder in the evaluation of patients with unexplained syncope. *Heart Rhythm*. 2011;8:858–863.
43. Vavetsi S, Nikolaou N, Tsarouhas K, et al. Consecutive administration of atropine and isoproterenol for the evaluation of asymptomatic sinus bradycardia. *Europace*. 2008;10:1176–1181.
44. Fujimura O, Yee R, Klein GJ, Sharma AD, Boahene KA. The diagnostic sensitivity of electrophysiologic testing in patients with syncope caused by transient bradycardia. *N Engl J Med*. 1989;321:1703–1707.